210. *Metal Ions and Complexes in Organic Reactions. Part I. Substitution Reactions between Aryl Halides and Cuprous Salts in Organic Solvents.*

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Quantitative studies are reported for substitutions of the type ArHal + CuX $\longrightarrow$ ArX + CuHal, effected at 110—140° in polar organic solvents. Some of the processes have preparative value. No salts other than those of copper were effective. Ease of displacement followed the orders: Hal = I, Br > Cl $\gg$ F; X = Cl > Br > I > CN, SPh > SCN. For a particular substitution, second-order rate constants varied by a factor of ~200 for a range of thirteen solvents. Some ligand-forming anions and heterocyclic bases caused inhibition. For bifunctional compounds, $Y{\cdot}C_6H_4{\cdot}Hal$, the reactions were relatively insensitive to the nature and positions of the nuclear substituents Y, except that a strong accelerating effect was observed for an *o*-nitro-group. The results are interpreted in terms of bimolecular reactions between the aryl halide and cuprous salt, and of competition between ligands in intermediate copper(I) complexes. The reactions are discussed in relation to existing knowledge of solute species in copper(I) solutions and of postulated mechanisms of nucleophilic aromatic substitutions.

In their comprehensive review[1] of aromatic nucleophilic substitutions, Bunnett and Zahler referred to the uncertain mechanism of reactions promoted by transition metals and their salts, among which copper(I) compounds are predominant. The best-known examples are the Sandmeyer and the Ullmann reactions, the former of which has been discussed in detail by Cowdrey and Davies.[2] Since the publication of these reviews there have been substantial developments[3] in the study of non-catalysed aromatic nucleophilic substitutions, particularly those involving reactions in solutions between activated aryl halides and, *e.g.*, amines, alcohols, and alkali-metal salts, but substitutions in which transition-metal compounds are reagents have attracted much less attention. Our own interest in this field began with a study of copper(I)-promoted introduction of hydrogen in place of halogen in aryl halides; this is described in Part III.[4] Other kinds of copper(I)-promoted replacements were concurrently studied, under homogeneous or heterogeneous conditions; examples of the former are discussed in this paper, and examples of the latter in Part II.[5] Summaries of the investigations at an earlier stage have appeared elsewhere.[6]

The reactions discussed in this paper, ArHal + CuX $\longrightarrow$ ArX + CuHal, are carried out in an organic solvent, the nature of which has a large effect on the ease of the substitution. The most accessible cuprous salts are the chloride, bromide, iodide, cyanide, thiocyanate, and (by preparation from thiols) thiophenoxides. The best-known application of their reactions with aryl halides is in the preparation of aryl cyanides from cuprous cyanide,[7] traditionally effected in pyridine or another heterocyclic base at 150—250°. With the above-named cuprous salts substitution occurred particularly readily between aryl halides and cuprous halides. This kind of halogen exchange is not well known. Recently, it was exemplified[8] by preparations of chloro-compounds, *e.g.*, by reaction in α-picoline between cuprous chloride and bromo-derivatives of polycyclic

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[1] Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 273.
[2] Cowdrey and D. S. Davies, *Quart. Rev.*, 1952, **6**, 358.
[3] See, *e.g.*, Bunnett, *Quart. Rev.*, 1958, **12**, 1, and later publications.
[4] Bacon and Hill, *J.*, 1964, 1112.
[5] Bacon and Hill, following paper.
[6] Bacon and Hill, *Proc. Chem. Soc.*, 1962, 113; Proceedings of the Seventh International Conference on Coordination Chemistry, Stockholm, June 1962, p. 262.
[7] Kurtz, in Houben-Weyl, " Methoden der Organischen Chemie," 4th edn., 1952, Vol. 8, Part III, p. 302; Mowry, *Chem. Rev.*, 1948, **42**, 189.
[8] Hardy and Fortenbaugh, U.S.P. 2,769,815; *J. Amer. Chem. Soc.*, 1958, **80**, 1716.

quinones, and it was observed[9,10] as a side-reaction during the nuclear coupling of aryl halides with copper.

RESULTS

Reaction of 1-*Halogenonaphthalenes with Cuprous Salts.*—The conversion of 1-bromo- into 1-chloro-naphthalene by cuprous chloride was a convenient example for study. For ordinary nucleophilic replacements with bromonaphthalene, temperatures of 200—300° are prescribed, but the reaction with cuprous chloride went readily to completion, in various solvents, at 110—190°, and was suitable for preparative purposes. For example, labelled 1-chloronaphthalene was made in one hour by reaction of 1-bromonaphthalene with the radioactive chloride, $Cu^{36}Cl$, in boiling dimethyl sulphoxide. When the substitutions were not carried to completion, the resulting mixtures of 1-chloro- and 1-bromo-naphthalene were best analysed by gas chromatography. Calibration runs established that the two halides could then be estimated with an accuracy of ±2%. By analysis of samples from reaction mixtures, containing known concentrations of an inert hydrocarbon, such as biphenyl, as an internal standard, it was established that the disappearance of 1-bromonaphthalene was normally accompanied by the appearance of a corresponding amount of 1-chloronaphthalene. Nuclear coupling, *i.e.*, the production of 1,1′-binaphthyl, was never detected, and reduction to naphthalene was observed as a subsidiary reaction only when the solvent was pyridine *N*-oxide (see below).

TABLE 1.

$1\text{-}C_{10}H_7Hal$ (0·08M) + CuX (0·8M) ⟶ $1\text{-}C_{10}H_7X$ + CuHal (in pyridine at 115° for 24 hr.).

X	Cl	Cl	Cl	Cl	Br	Br	I	I	CN	CN	SPh	SCN
Hal	F	Cl *	Br	I	Cl	I	Cl	Br	Br	I	Br	Br
$1\text{-}C_{10}H_7X$ (%)	Nil	5	84	100	5	100	Nil	30	24	100	26	~10 †

* $1\text{-}C_{10}H_7{}^{36}Cl$, from $Cu^{36}Cl$. † Impure sulphur-containing solid, probably naphthyl sulphides.

TABLE 2.

Reactions at 115° ($1\text{-}C_{10}H_7Br$, 0·083M; in pyridine) and 110° ($1\text{-}C_{10}H_7Br$, 0·080M; in dimethyl sulphoxide).

CuCl (M)		0·83	0·56	0·50	0·33	0·20	0·17	0·12	0·08
10^5k (l. mole^{-1} sec.$^{-1}$)	115°	3·3	—	4·0	5·0	—	6·2	—	—
	110°	—	23	—	—	28	—	30	29

It had previously been reported[11] that equilibria are established in substitution reactions between activated aryl halides, such as halogeno-2,4-dinitrobenzenes, and alkali-metal halides. The relative ease of halogen displacement in ArHal–CuHal′ systems was tested by treatment of 1-fluoro-, 1-chloro-, 1-bromo-, or 1-iodo-naphthalene with a ten-fold excess of cuprous chloride, bromide, or iodide in refluxing pyridine. The chloride–chloride exchange was followed by using the system 1-chloronaphthalene–cuprous [^{36}Cl]-chloride and measuring the radioactivity of isolated samples of the chloronaphthalene. Results of typical experiments are shown in Table 1, together with data for similar reactions of cuprous cyanide, thiocyanate, and thiophenoxide. These results show that the ease of displacement of halogen from the nucleus is in the order $I > Br > Cl \gg F$, and that the ease of entry of the nucleophile from the cuprous salt is in the order $Cl > Br > I > CN, SPh > SCN$. It had previously been reported[12] that cuprous thiocyanate gives a diaryl disulphide or monosulphide, rather than an aryl thiocyanate, with an aryl

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[9] Nilsson, *Acta Chem. Scand.*, 1958, **12**, 537.
[10] Forrest, *J.*, 1960, 589.
[11] Bennett and Vernon, *J.*, 1938, 1783.
[12] Rosenmund and Harms, *Ber.*, 1920, **53**, 2226; cf. Miller *et al.*, ref. 39.

halide in pyridine. This result is probably explained by the observation that amines cause fission of the ArS–CN bond when heated with aryl thiocyanates.[13]

In the halide-exchange reactions, the poor conversion observed in the aryl chloride–cuprous bromide system, even when the cuprous bromide was in large excess, suggested that production of chloro-compound in the aryl bromide–cuprous chloride system should not be complicated to any marked extent by reversibility. In studying the latter system, an excess of cuprous chloride (2- to 5-fold) was usually employed, and reaction rates were in fact found to be accurately proportional to $(a - x)(b - x)$, where (when Ar = 1-naphthyl) a was the initial concentration of cuprous chloride, b was the initial concentration of 1-bromonaphthalene, and x was the observed concentration of the resulting 1-chloronaphthalene. Straight-line plots of log $[(a - x)/(b - x)]$ were normally observed throughout the course of the reactions (Fig. 1), and second-order rate constants, thus derived, are shown in the Tables. Rate measurements were commonly made with concentrations of cuprous halide appropriate for preparative work. In this range (0·2—1·0M) there was a slight rise in the value of k with diminishing concentration, reasonable constancy being obtained at greater dilution; this is illustrated in Table 2.

TABLE 3.

Reactions at 110·5° (1-$C_{10}H_7Br$, 0·1M; CuCl, 0·4M) and 144·5° (1-$C_{10}H_7Br$, 0·1M; CuCl, 0·2M). The column headed R.E. contains figures for the relative effects of solvents in alkylations (Zaugg *et al.*, 1960; ref. 14).

Solvent	ε	10^5k (l. mole^{-1} sec.$^{-1}$) 110·5°	10^5k (l. mole^{-1} sec.$^{-1}$) 144·5°	R.E.
Quinoline	9·0	0·1	6·7	—
α-Picoline	9·6	0·1	—	—
Benzonitrile	26	0·2	—	3·0
s-Collidine	—	0·4	6·4	—
γ-Picoline	—	1·8	—	—
Pyridine	12·3	1·9 *	—	1·0
Dimethylacetamide	38	9·5 *	140	6·5
Hexamethylphosphoramide	—	11·5	130	40
N-Methyl-2-pyrrolidone	—	12·0 *	190	8·1
Dimethylformamide	37	12·0 †	260	5·8
N-Methyl-2-pyridone	—	16·5	— ‡	12·0
Dimethyl sulphoxide	45	25 *	360	11·5
Pyridine *N*-oxide	—	— §	600 §	14·0

* Values in the system 1-$C_{10}H_7Br$ (0·08M)–CuCl (0·08M) were 2·5, 16, 19, and 28, respectively. † The system was heterogeneous; solubility limit = 0·20M at 110°. ‡ Reaction showed deviation from second-order kinetics. § Reaction accompanied by reduction (Fig. 2).

Table 3 shows variations in the rate constant for thirteen organic solvents which dissolve cuprous chloride; the extremes vary by factors of ~250 and 100, at 110 and 144°, respectively. Reported data[14] are included in Table 3 to illustrate the relative efficacy of the same solvents in promoting nucleophilic substitutions of alkyl halides (see p. 1104).

Fig. 1 illustrates the second-order reaction-rate plots which were obtained in most solvents for aryl halide–cuprous chloride substitutions. Deviation from the straight-line relationship was shown by *N*-methyl-2-pyridone at 144·5°. A second anomalous solvent (Fig. 2) was pyridine *N*-oxide, in which displacement of bromine from 1-bromonaphthalene by hydrogen competed with its displacement by chlorine; Fig. 2 incidentally illustrates the rapidity of copper(I)-promoted exchange in a good solvent. The reduction is discussed in Part III.[5]

The aryl halide–cuprous salt reactions are subject to inhibition, as is shown by the following examples. The second-order rate constant (32×10^{-5} l. mole^{-1} sec.$^{-1}$) observed for the reaction of 1-bromonaphthalene (0·15M) with cuprous chloride (0·15M) in dimethyl sulphoxide at 110·5° (cf. Table 3) was reduced to 5×10^{-5} by inclusion of pyridine (0·6M) and to $1·5 \times 10^{-5}$ by inclusion of 2,2′-bipyridyl (0·3M). The same reaction in pyridine at 110·5° (Table 3) deviated from second-order kinetics when lithium chloride was included

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[13] Hoggarth and Sexton, *J.*, 1947, 815.
[14] Zaugg *et al.*, *J. Amer. Chem. Soc.*, 1960, **82**, 2895, 2903; 1961, **83**, 837.

in the solution and was completely suppressed when the LiCl : CuCl molar ratio was raised to 16. Suppression of the reaction was also observed in dimethyl sulphoxide solutions containing potassium fluoride (KF : CuCl molar ratio, 4); half of the cuprous ion was removed from solution and appeared in a fluoride-containing precipitate of uncertain composition. Likewise, at 144·5° in dimethylformamide, the reaction of 1-bromonaphthalene with the sparingly soluble cuprous thiophenoxide was strongly affected by addition of sodium thiophenoxide (CuSPh : NaSPh molar ratio, 0·5); the system became homogeneous and the yield of 1-naphthyl phenyl sulphide fell from 30 to 2%.

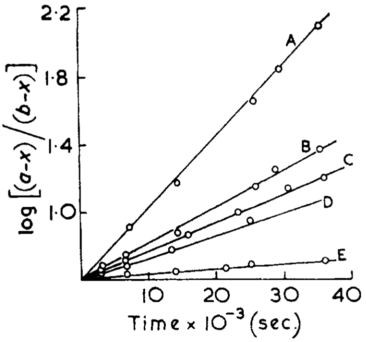


FIG. 1. 1-$C_{10}H_7Br$ + CuCl at 110·5° in A dimethyl sulphoxide, B dimethylformamide, C *N*-methyl-2-pyrrolidone, D *p*-NO_2·C_6H_4Br + CuCl at 110·5° in pyridine; E pyridine.

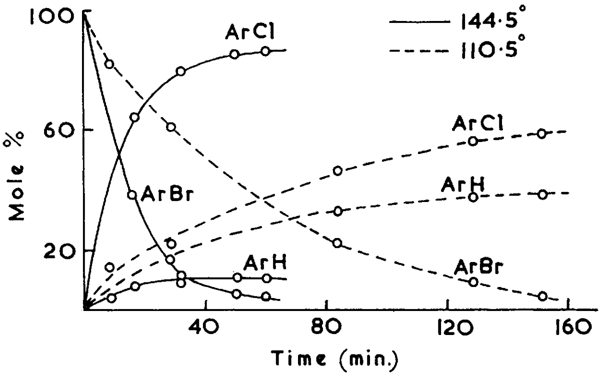


FIG. 2. Halogen exchange and reduction: 1-$C_{10}H_7Br$ (ArBr) + CuCl in pyridine *N*-oxide (Table 3).

TABLE 4.

Reaction of 1-bromonaphthalene with cuprous cyanide.

Initial concn. (M) of 1-$C_{10}H_7Br$	0·1	0·1	0·1	0·15	0·2
Initial concn. (M) of CuCN	0·2	0·15	0·1	0·1	0·1
10^4k (l. mole^{-1} sec.$^{-1}$)	3·5 ± 0·15	4·05 ± 0·25	4·4 ± 0·2	4·8 ± 0·2	4·6 ± 0·0

Under the conditions examined, the reaction of 1-bromonaphthalene with cuprous cyanide was more complicated kinetically than the corresponding reaction with cuprous chloride. Second-order constants, calculated at different times, showed an increase as the reaction proceeded, but tended towards constancy in its later stages; the deviation was least when the initial concentration of cuprous cyanide was least. The figures in Table 4 show results in dimethyl sulphoxide at 144·5°, calculated from analyses of samples withdrawn after ~50% of this halide had reacted. Comparison with the corresponding values for cuprous chloride (Table 3) indicates that the latter is about six times as reactive as the cyanide.

TABLE 5.

Substitution effects.

(*a*) 10^5k (l. mole^{-1} sec.$^{-1}$) for X·C_6H_4Br (0·1M) + CuCl (2 mol.) in pyridine at 110·5°.

X = *p*-OMe	*o*-Me	*p*-Me	H	*m*-NO_2	*p*-NO_2	*o*-NO_2
1·7	1·7	2·2	2·4	6·0	10·2	1000

(*b*) 10^5k (l. mole^{-1} sec.$^{-1}$) at 110·5° for *p*-NO_2·C_6H_4Hal (0·1M).

With CuCl (4 mol.) in pyridine: I, 9; Br, 10; Cl,* 0·2.
With CuCl (2 mol.) in dimethyl sulphoxide: I, 52; Br, 64; Cl,* 0·9.

* $Cu^{36}Cl$ used.

Substitution Effects.—For nuclear substituted aryl halides, the effect of the substituents on the rate of halogen exchange with cuprous chloride differs very greatly from the effect of these substituents on the rate of reaction of the halides with common nucleophiles. This is illustrated for some benzene derivatives in series (*a*) of Table 5. The reactivity shown for bromobenzene (X = H) was about the same as that observed for 1-bromonaphthalene under similar conditions (Table 3). Series (*b*) shows the relative ease of displacement of chlorine, bromine, and iodine in *p*-nitrophenyl halides. For chloride–chloride exchange, the system p-$NO_2 \cdot C_6H_4Cl$–$Cu^{36}Cl$ was used, the reference sample of nitro-[^{36}Cl]halide having been obtained by treatment of *p*-bromonitrobenzene with radioactive cuprous chloride in refluxing dimethyl sulphoxide. The relative effect of the two solvents on reaction rates in this series, *i.e.*, rate (dimethyl sulphoxide)/rate (pyridine) ~ 5, was smaller than that observed in the reaction of 1-bromonaphthalene with cuprous chloride (Table 3).

The reverse reaction, *i.e.*, replacement of nuclear chlorine by bromine, was difficult, as in the case of unsubstituted aryl chlorides. Not more than 1% replacement was detected in chlorobenzenes, p-$X \cdot C_6H_4Cl$ (X = H, Me, OMe, NO_2), after treatment of 0·1M-pyridine solutions with cuprous bromide (4 mol.) for 24 hr. at 110°.

The Special Reactivity of Copper(I) *Salts.*—Lithium chloride, as an example of an alkali-metal halide, was examined with aryl halides in pyridine at 110°. No halogen replacement was observed with 1-bromonaphthalene, with *p*-fluoro-, *p*-bromo-, or *p*-iodo-nitrobenzene, or with *o*-bromonitrobenzene. The non-reactivity towards 1-bromonaphthalene in boiling pyridine was not overcome by the addition of cuprous chloride in small amounts (6 mole %), or, in dimethyl sulphoxide at 144°, by the addition of an equivalent amount of metallic copper.

Solutions of anhydrous silver, gold(I), thallium(I), zinc, mercury(II), iron(II), and cobalt(II) chlorides were also examined with 1-bromonaphthalene in pyridine at 110°; in the case of silver, the halide was mainly in suspension (solubility, 0·12 g. in 100 g. of pyridine at 110°). In none of these experiments was more than 0·1% of 1-chloronaphthalene indicated by analysis after 10 hours. Replacement also failed with iron(II) chloride in dimethylformamide at 144° and with gold(I) chloride in dimethyl sulphoxide at 110°. The gold(I) chloride showed disproportionation, $3Au^+ \longrightarrow 2Au + Au^{3+}$, yielding a precipitate of metallic gold, both in pyridine and in dimethyl sulphoxide. In the latter case there was also a sublimate of polymeric formaldehyde which resulted from a reaction involving the solvent. Silver cyanide and nickel(II) cyanide failed to give 1-cyanonaphthalene when used as suspensions in dimethyl sulphoxide solutions of 1-bromonaphthalene at 144°.

Some variations in the employment of copper salts were tried. Anhydrous copper(II) chloride did not react with 1-bromonaphthalene in dimethyl sulphoxide at 110°, but 1-chloronaphthalene (50%) was obtained after 24 hr. by reaction in boiling pyridine, together with much tar. A mixture of copper(II) chloride and metallic copper gave the chloro-compound in 80% yield under similar conditions.

DISCUSSION

It is necessary to account for the following features of the aryl halide–cuprous salt reactions studied. (i) Within the range of compounds and conditions examined, copper salts are uniquely reactive. (ii) Kinetic data suggest bimolecular reactions between the aryl halide and the cuprous salt. (iii) Reaction rates may vary by a factor of ~200, depending on the nature of the solvent. (iv) Addition of ligand-forming ions or heterocyclic bases causes inhibition. (v) Ease of displacement of halogen from the aryl nucleus is in the order I, Br $>$ Cl $\gg$ F. (vi) Ease of entry into the nucleus of a substituent X from CuX is in the order Cl $>$ Br $>$ I $>$ CN, SPh $>$ SCN. (vii) Variation of *para*-substituents in the aryl halide has a very small effect on the reaction rate (only ~5-fold increase for p-NO_2). A strong accelerating effect is observed for an *o*-nitro-substituent.

So far as copper salts are concerned, discussion may be confined to the copper(I) series. Although copper(II) chloride caused replacement of bromine in bromonaphthalene under some conditions, this was not necessarily due to the bivalent metal, since copper(II) halides fairly readily halogenate aromatic compounds in solution,[15] and thereby become univalent. Unique reactivity is not invariably found for copper(I) compounds in metal-assisted aromatic replacements. For example, salts of other transition metals are sometimes effective in Sandmeyer reactions,[3] and, at 200°, the chlorides of silver and other metals are not greatly inferior to cuprous chloride[16] in promoting the replacement: $PhCl + NH_2Me \longrightarrow Ph{\cdot}NHMe$. In our own experiments, silver chloride differed from the other salts in being sparingly soluble. It is known, however, that its insolubility does not preclude halogen exchange in alkyl bromide–silver chloride systems involving reactive bromides.[17] Comparison with gold(I) is invalidated by the ready disproportionation, $3Au^+ \longrightarrow 2Au + Au^{3+}$, which we observed. For the reactions under discussion, copper(I) is therefore exceptional in performance even among members of its own group in the Periodic Table.

Within the range of conditions which we used, a variety of copper-containing molecular species may be postulated. Thus, cuprous chloride may occur in the following forms, depending upon the degree of its solvation by ligand-forming solvent molecules, L: solid $(CuCl)_n$ (reaction at solid–solvent interface); $(CuCl)_xL_y$ (solvated polymeric solute); CuClL, $CuClL_2$, $CuClL_3$ (monomeric complexes); $CuL_4^+\,Cl^-$ or $CuL_z^+\,Cl^-$ (ion pairs with tetrahedral or indefinite solvation of the cation). Change of solute species within this series may be the explanation of the observed differences in rate constant in solutions of different concentrations (Table 2).

Limited information is available in the literature concerning these alternatives. An equilibrium between dimeric and monomeric molecules was suggested, many years ago, to explain results of ebullioscopic measurements with solutions of cuprous halides or cyanide in pyridine, quinoline, and other solvents.[18] Recent data obtained at high temperatures for the vapour suggest that a cyclic trimer, rather than a dimer, is the polymeric form of the chloride.[19] For cuprous halides or cyanide, evidence for ionic species in organic solvents is not available, *e.g.*, from conductivity data, such as exist for some other transition-metal salts.[20]

Crystalline copper(I) complexes are known,[21] in which the metal atom is co-ordinated with one, two, or three molecules of heterocyclic bases, organic cyanides, and other solvents. Copper(I) derivatives are not represented, however, in the series of crystalline complexes reported for several transition-metal salts with dimethyl sulphoxide,[22] and with pyridine *N*-oxide,[23] *i.e.*, with solvents in which replacements proceeded most readily in our experiments (Table 3). Ionic copper(I) complexes occur,[21] *e.g.*, as $CuL_4^+\,Cl^-$ (L = thioacetamide) and $CuL_3^+\,Cl^-$ (L = thiourea); the species $Cu(MeCN)_4^+\,X^-$ ($X = NO_3$, ClO_4, or BF_4), dissociate completely into Cu^+ and X^+ ions in methyl cyanide solution.[24]

We assume that our experiments have commonly involved a monomeric cuprous salt, associated with a mobile population of tetrahedrally co-ordinated ligands. We also assume, as has been done previously[1,25] for reactions of this type, that substitution is

[15] Ware and Borchert, *J. Org. Chem.*, 1961, **26**, 2263, 2267; Kochi, *J. Amer. Chem. Soc.*, 1962, **84**, 2121.

[16] Hughes, Veatch, and Elersich, *Ind. Eng. Chem.*, 1950, **42**, 787.

[17] See, *e.g.*, Gomberg, *Ber.*, 1902, **35**, 1822; Schlubach, Stadler, and Wolf, *ibid.*, 1928, **61**, 287; Ness, Fletcher, and Hudson, *J. Amer. Chem. Soc.*, 1951, **73**, 959.

[18] Werner *et al.*, *Z. anorg. Chem.*, 1897, **15**, 1; Beckmann and Gabel, *ibid.*, 1906, **51**, 236.

[19] Brewer and Lofgren, *J. Amer. Chem. Soc.*, 1950, **72**, 3038; Wong and Schomaker, *J. Phys. Chem.*, 1957, **61**, 358; Shelton, *Trans. Faraday Soc.*, 1961, **57**, 2113.

[20] C. W. Davies, " Ion Association," Butterworths, London, 1962; Prue and Sherrington, *Trans. Faraday Soc.*, 1961, **57**, 1795.

[21] Gmelins Handbuch der Anorganischen Chemie, Copper, System, No. 60, Part B, Section 1, 1958.

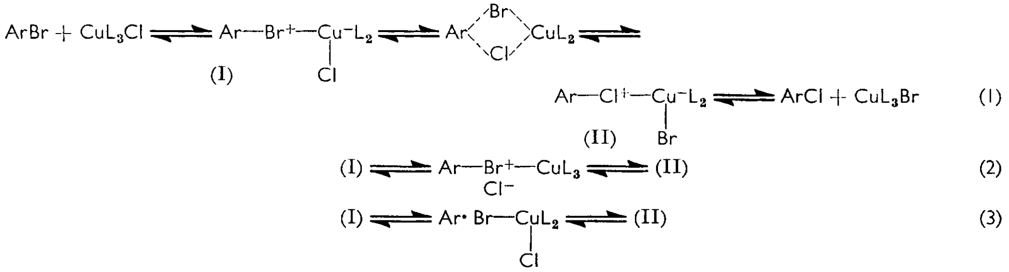
[22] Schläfer and Schaffernicht, *Angew. Chem.*, 1960, **72**, 618; Cotton and Francis, *J. Amer. Chem. Soc.*, 1960, **82**, 2986; Meek, Straub, and Drago, *ibid.*, p. 6013.

[23] Quagliano, Fujita, Franz, Phillips, Wamsley, and Tyree, *J. Amer. Chem. Soc.*, 1961, **83**, 3770; Carlin, *ibid.*, p. 3773.

[24] Hathaway, Holah, and Postlethwaite, *J.*, 1961, 3215.

[25] Koelsch and Whitney, *J. Org. Chem.*, 1941, **6**, 795.

preceded by bonding between the copper atom and the halogen of the aryl halide, giving an " onium " structure (I). Preliminary experiments, designed to detect such complexes by solubility measurements, were unsuccessful. Complexes of silver ion with an aromatic nucleus are well known, and the effect of silver nitrate in increasing the aqueous solubility of phenyl halides has been attributed [26] to π-complexing of Ag^+ with the aromatic ring for chloro- and bromo-benzene, and to a halogen-bonded complex, $Ph{-}I^+{-}Ag$, for iodobenzene. A recent determination [27] of the crystal structure of the complex $CuAlCl_4,C_6H_6$ provides evidence, possibly for the first time, of π-bonding between copper(I) and an aromatic ring. Only speculative views can be advanced, however, concerning the nature of aryl halide–copper(I) bonding in organic solvents and concerning the unique catalytic property of the metal in this situation. Three ways of representing bond-breaking in an intermediate complex such as (I) are shown below. (The number of solvent-molecule ligands is shown as two or three, as required to maintain a four-co-ordinate state.)



In view of the observed dependence of the rate of substitution on the nature of the solvent, the four-centre process (1), having no discrete ionisation step, might be thought unlikely. However, the nature of the solvent does have a substantial influence in some reactions believed to be of the four-centre type, *i.e.*, Diels–Alder additions,[28] Claisen rearrangements,[29] and hydroboration.[30] Four- or six-centred transition states have been suggested for replacements involving Ar–Hg and Ar–Si bonds.[31]

Multi-centre processes are not sharply differentiated from those with an intermediate ionic state, such as (2). Here, the dissociation of the complex (I) is shown as the source of chloride ion, but alternatively, in ionising solvents, it might be initially present in ion pairs, $CuL_4^+ Cl^-$. The greater reactivity between (I) and Cl^-, as compared with that between ArBr and Cl^-, is in harmony with the trend, $ArX^+ > ArX > ArX^-$, found for other nucleophilic aromatic substitutions.[32]

Route (3) involves a homolytic fission, giving an intermediate copper(II) species and an aryl radical, which is presumed, as in discussions of some other postulated homolytic reactions, not to escape its " solvent cage." This view, which relates the efficacy of copper to its ready transition between univalent and bivalent states, is analogous to interpretations given for the Sandmeyer reaction,[2,33] and for the Meerwein arylation reaction.[34] Biaryls, attributed to radical coupling, are by-products of some Sandmeyer reactions, but have not been reported for Meerwein reactions; they were not observed in the aryl halide reactions, though it has subsequently been found [35] that copper(I) compounds are efficient in promoting α-carbon coupling in reactive arylalkyl halides, such as

[26] Andrews and Keefer, *J. Amer. Chem. Soc.*, 1950, **72**, 3113.

[27] Amma and Turner, *J. Amer. Chem. Soc.*, 1963, **85**, 4046.

[28] Wassermann, *J.*, 1942, 623.

[29] J. Hine, " Physical Organic Chemistry," 2nd edn., McGraw-Hill, New York, 1962, p. 505.

[30] H. C. Brown, " Hydroboration," W. A. Benjamin Inc., New York, 1962.

[31] Dessy and Lee, *J. Amer. Chem. Soc.*, 1960, **82**, 689; Stock and Brown, *Adv. Phys. Org. Chem.*, 1963, **1**, 41.

[32] Bolto and Miller, *Austral. J. Chem.*, 1956, **9**, 74.

[33] Nonhebel and Waters, *Proc. Roy. Soc.*, 1957, *A*, **242**, 16; *Adv. Catalysis*, 1957, **9**, 353.

[34] Rondestvedt, *Org. Reactions*, 1960, **11**, 189; Schrauzer, *Chem. Ber.*, 1961, **94**, 1891.

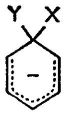
[35] Bacon and Stewart, unpublished data.

diphenylmethyl chloride. However, the occurrence of coupling is an uncertain diagnostic test for homolytic reactions.

Irrespective of the nature of the bond-breaking step in the ArHal–CuX reactions, the concept of competition between ligands in copper(I) complexes is consistent with features summarised in (i)—(vii) above. The observed relative affinity of the halogens for the metal (v and vi), is in accordance with the classification of copper(I) as a class (*b*) metal.[36] The greater difficulty of the replacements involving entry of CN, SPh, or SCN instead of halogens (vi) is reflected in the higher stability constants quoted [37] for copper(I) complexes with CN (log β_2 $\sim$16) and sulphur-containing ligands ($\sim$12—15), as compared with corresponding constants for the halogens (Cl $\sim$5, Br $\sim$6, I $\sim$8). The marked susceptibility of the substitutions to inhibition (iv) is explicable if the chances of bonding between aryl halide and metal are reduced by the presence of strongly bound solvent molecules, or of anions which give species such as $CuCl_2^-$ and $Cu(SPh)_2^-$. The greater efficacy of 1,1′-bipyridyl as an inhibitor, compared with pyridine, is reflected in the different stability constants of their copper(I) complexes (log β_2 $\sim$14 and $\sim$3, respectively). Divergences noted in the kinetics of the reaction $ArBr + CuCN \longrightarrow ArCN + CuBr$ may be connected with the strong ligand-forming properties of the product aryl cyanide and with differences in catalytic effect of the product cuprous bromide compared with the reagent cuprous cyanide.

Variation in ligand-forming capacity is presumably one reason for the large solvent effect (iii) observed in halide replacements. Within the group of heterocyclic basic solvents (Table 3), which are known to be good ligands for copper(I), lowest reaction rates are associated with 2-substituted pyridine rings. Possibly a steric factor is operating, as has been suggested to explain differences between these bases in relation to other metal complexes.[38] Another cause of the solvent effect may be the ability of the most favourable solvents (Table 3) to promote the ionic dissociation involved in the substitution route (2) shown above. Zaugg and his co-workers [14] observed acceleration effects, comparable to those which we report, when they added a similar series of solvents to benzene solutions containing alkyl halides and malonate carbanions as reagents: $AlkBr + Na^+R^- \longrightarrow AlkR + Na^+Br^-$. They ascribed this effect to solvation of sodium ions, with consequent dissociation of ion-pair aggregates. As Table 3 shows, the relative order of solvent activity which they observed corresponds to ours in some cases but not in others.

The fact that the aryl halide–cuprous salt substitutions are relatively insensitive to the presence and nature of *para*- or *meta*-substituents (vii) demonstrates that these reactions do not proceed through charged intermediates of type (III), which are postulated [3] for reactions of activated aryl halides with ordinary nucleophiles. The usual order of reactivity for nuclear halogen in reactions of activated aryl halides is $F \gg Cl \sim Br \sim I$. Moreover, the latter reactions are strongly contrasted kinetically with the copper-promoted reactions, since the presence of electron-attracting *para*-substituents increases their second-order rate constants enormously,[39] *e.g.*, by factors of 10^4—10^9. On the other hand, the case of *o*-bromonitrobenzene (Table 5) suggests that fairly strong activation may result from the presence of an unsaturated *ortho*-substituent in copper-promoted reactions; this is being studied further. Other examples of exceptional reactivity in *ortho*-substituted halides are known for nucleophilic aromatic substitutions;[3,40] it has been discussed [3] as a " built-in solvation " effect.



(III)

The practical value so far found for aryl halide–cuprous salt reactions may thus be summarised. Conversion of an aryl bromide or iodide into the chloride, though not often

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[36] Ahrland, Chatt, and N. R. Davies, *Quart. Rev.*, 1958, **12**, 265.
[37] " Stability Constants," *Chem. Soc. Special Publ.*, Nos. 6 and 7, Part I, 1957; Part II, 1958.
[38] Cf. Sacconi, Lombardo, and Paoletti, *J. Inorg. Nuclear Chem.*, 1958, **8**, 217.
[39] *E.g.*, Bevan and Bye, *J.*, 1954, 3091; Miller, Parker, and Bolto, *J. Amer. Chem. Soc.*, 1957, **79**, 95.
[40] Greizerstein and Brieux, *J. Amer. Chem. Soc.*, 1962, **84**, 1032.

required in preparative work, is easily effected. The conversion of a halide into the cyanide[7] is much improved by selection of a suitable solvent, such as dimethyl sulphoxide (cf. Table 3); other workers[41] have recently recommended dimethylformamide and *N*-methylpyrrolidone. Conversion of a halide into a diaryl sulphide was only moderately effective and could probably be improved by variation in conditions (cf. preparations of alkyl aryl sulphides[42]), but it is better carried out by the alternative process with cuprous oxide.[5] The conversion of a halide into the thiocyanate is slow, and deviates to sulphide or disulphide formation; this is a common difficulty in preparations of aryl thiocyanates.

EXPERIMENTAL

Solvents.—AnalaR pyridine was dried over potassium hydroxide, redistilled, and, for kinetic experiments, further purified through its zinc chloride complex.[43] α-Picoline was redistilled after steam-distillation of an acidic solution.[43] γ-Picoline was purified[43] through its zinc chloride complex, and by distillation and freezing. Quinoline was purified through its zinc chloride complex. *s*-Collidine was redistilled after refluxing over barium oxide. Dimethylformamide, dimethylacetamide, and dimethyl sulphoxide were treated with barium oxide and redistilled under nitrogen they were stored over calcium hydride or molecular sieve (Linde type 5 A), and were redistilled under nitrogen just before use. *N*-Methyl-2-pyrrolidone was dried by azeotropic distillation with benzene and fractionally distilled under nitrogen. *N*-Methyl-2-pyridone[44] and pyridine *N*-oxide[45] were prepared by standard methods. For the preparation of hexamethylphosphoramide, a benzene solution of chlorotetramethylphosphonamide (Albright and Wilson) was treated with dimethylamine (2 equiv.), the precipitated dimethylamine hydrochloride was filtered off, and the triamide, b. p. 70°/1 mm., n_D^{18} 1·4599, was purified by distillation.

Copper(I) *Salts.*—AnalaR cuprous chloride was further purified.[46] Cuprous cyanide was dried by adding benzene and distilling off the benzene–water azeotrope, and by keeping the salt at 100°/0·1 mm. for 24 hr. Cuprous thiophenoxide was prepared by the method of Adams *et al.*[42]

Reagents Containing ^{36}Cl.—Hydrochloric acid (1·6N) containing $H^{36}Cl$ was supplied by the Radiochemical Centre, Amersham. Seventy-fold dilution with ordinary hydrochloric acid and neutralisation with sodium hydroxide provided 100 ml. of an aqueous solution of sodium chloride (0·11 mole) containing $Na^{36}Cl$, to which were added solutions of copper sulphate (0·1 mole), sodium hydrogen sulphite (0·05 mole), and sodium hydroxide (0·09 mole) at 60°. The precipitated cuprous chloride was isolated by cooling the mixture, washing the precipitate (by decantation) with aqueous sulphur dioxide solution, collecting on a sintered-glass filter, washing successively with acetic acid and ethanol, and drying at 100°/1 mm. The product, containing $Cu^{36}Cl$, showed $3{\cdot}45 \times 10^4$ counts/100 sec./0·1 g.; an end-window Geiger counter coupled with an Ecko automatic scalar was used for measurements of radioactivity.

To prepare [1-^{36}Cl]chloronaphthalene, a solution of 1-bromonaphthalene (0·01 mole) and the radioactive cuprous chloride (0·011 mole) in dimethyl sulphoxide (25 ml.) was heated under reflux in an atmosphere of nitrogen for 1 hr., then added to 6N-hydrochloric acid, and the product extracted with ether. After washing with water, drying, and distillation, the extract gave [1-^{36}Cl]chloronaphthalene, b. p. 63°/0·3 mm., n_D^{18} 1·6342, in nearly quantitative yield; it showed 16,200 counts/100 sec./0·1 g. Gas chromatography showed that its content of 1-bromonaphthalene was negligible.

A similar method was used to convert *p*-bromonitrobenzene into [*p*-^{36}Cl]chloronitrobenzene. The product (95%), m. p. 82—83°, showed 24,600 counts/100 sec./0·1 g.

Reactions of Aryl Halides with Copper(I) *Salts.*—All reactions with cuprous salts were carried

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[41] Newman and Phillips, *J. Amer. Chem. Soc.*, 1959, **81**, 3667; Newman and Boden, *J. Org. Chem.*, 1961, **26**, 2525; Friedman and Schechter, *ibid.*, p. 2522.

[42] Adams, Reifschnieder, and Nair, *Croat. Chem. Acta*, 1957, 29; Adams and Ferretti, *J. Amer. Chem. Soc.*, 1959, **81**, 4927.

[43] A. I. Vogel, " Practical Organic Chemistry," 3rd edn., Longmans, London, 1956.

[44] *Org. Synth.*, Coll. Vol. II, 419.

[45] Ochiai, *J. Org. Chem.*, 1953, **18**, 534.

[46] *Inorg. Synth.*, 1946, **2**, 1.

out in an atmosphere of oxygen-free nitrogen, and those involving rate measurements under conditions summarised in Tables 1—5.

Yields from experiments carried out in refluxing pyridine were determined by adding the cooled reaction mixture (150 ml.) to 6N-hydrochloric acid (300 ml.), extracting the product with benzene, washing and drying the extract, adding 1-methylnaphthalene as an internal standard, and analysing the solution by gas chromatography. Rate measurements, if required for reactions in refluxing pyridine, were carried out by withdrawing samples at intervals with a graduated syringe, and analysing them in a similar fashion; biphenyl, present during reaction, was also used as an internal gas-chromatography standard.

Most reaction-rate measurements were carried out with solutions of aryl halides in organic solvents (50 ml.) contained in a vapour-jacketed cylindrical Pyrex tube, shielded from the light, and kept at a constant temperature by boiling toluene (110·5°) or *o*-xylene (144·5°). The solid cuprous salt was initially sealed in a fragile glass bulb, which was broken in the solution by a stirrer when thermal equilibrium had been attained. The reaction vessel carried an upright condenser and was provided with a side-arm sealed by a rubber cap, through which samples were withdrawn with a graduated syringe. Cuprous chloride dissolved readily in the solvents studied, except that solution was incomplete in dimethylformamide. The solutions varied from practically colourless, *e.g.*, in dimethyl sulphoxide, to amber in pyridine and red in quinoline. Heating caused a little darkening in most solvents; *N*-methyl-2-pyrrolidone gave exceptionally dark solutions. The withdrawn samples (2 ml.) were added to 6N-hydrochloric acid (5 ml.), or to acidic ferric chloride in the experiments with cuprous cyanide, the organic product was extracted with benzene or ether, and the extract washed, dried, and analysed by gas chromatography.

Most analyses were carried out with a Pye Argon Chromatograph 12001. For halogenonitrobenzenes, to which this instrument did not respond reproducibly, a Griffin and George Mark IIA instrument was used. Compositions of mixtures were obtained by normalisation of peak areas given by the products, or by reference to an internal standard; the former method was frequently the more precise. Regular calibrations with mixtures of known composition were carried out.

Inhibition of Substitution Reactions.—Results are summarised above (p. 1099); see also the thiophenoxide data below. The brown solid, obtained when the 1-bromonaphthalene–cuprous chloride reaction in dimethyl sulphoxide was inhibited by potassium fluoride, was unstable and possibly variable in composition. About half of the cuprous ion was found in this precipitate, and half in solution. Fluorine analysis (by courtesy of Dr. A. M. G. Macdonald, Birmingham University) showed 24% present.

Reaction of 1-*Bromonaphthalene with Cupric Chloride.*—The anhydrous salt was prepared from the AnalaR hydrate.[47] An excess (0·125 mole) of this chloride, which did not completely dissolve, was used to treat 1-bromonaphthalene (0·0125 mole) for 24 hr. in boiling pyridine (150 ml.). The black viscous mixture gave a tarry product when added to 6N-hydrochloric acid. A benzene extract of this showed 1-chloronaphthalene (53%) and 1-bromonaphthalene (51%) when analysed by gas chromatography. A reaction carried out similarly, but with precipitated copper (0·125 g.-atom) also present, gave a cleaner product and showed an 80% yield of 1-chloronaphthalene. After 24 hr. at 110°, a solution of anhydrous cupric chloride (0·01 mole) and 1-bromonaphthalene (0·0025 mole) in dimethyl sulphoxide (150 ml.) contained 0·1 g. of cuprous ion according to volumetric analysis,[48] but 1-bromonaphthalene was recovered quantitatively.

Attempted Reactions with Chlorides of Other Metals (cf. p. 1099).—Commercial samples of lithium chloride, mercury(II) chloride, silver chloride, thallium(I) chloride, and zinc chloride were used. Anhydrous cobalt(II) chloride was prepared from its hydrate,[47] anhydrous iron(II) chloride from anhydrous iron(III) chloride,[49] and gold(I) chloride from tetrachloroauric acid.[50] In the experiment with gold(I) chloride in pyridine, the solution darkened considerably and deposited gold crystals within an hour. The same result was obtained in dimethyl sulphoxide, and on continued heating (13 hr.) a white sublimate of polymeric formaldehyde, m. p. 90—95°,

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[47] *Inorg. Synth.*, 1957, **5**, 153.

[48] Hatch and Estes, *J. Amer. Chem. Soc.*, 1945, **67**, 1730.

[49] *Inorg. Synth.*, 1960, **6**, 172.

[50] G. Brauer (editor), " Handbuch der Präparativen Anorganischen Chem," Enke Verlag, Stuttgart, 1954, p. 784.

appeared in the upper part of the apparatus. It was identified by depolymerisation at 150° and conversion of the formaldehyde vapour into the 2,4-dinitrophenylhydrazone, m. p. 166° (lit., 166°) (Found: C, 40·1; H, 2·8. Calc. for $C_7H_6N_4O_4$: C, 40·0; H, 2·8%).

Reaction of 1-*Bromonaphthalene with Cuprous Cyanide.*—(*a*) A solution of 1-bromonaphthalene (0·02 mole) and cuprous cyanide (0·22 mole) in dimethyl sulphoxide (50 ml.) was heated under reflux for 2 hr. For isolation of the product (cf. Friedman and Schechter [41]), the cooled solution was added to a solution of ferric chloride (60 g.) in 2N-hydrochloric acid (100 ml.) and extracted with benzene. Distillation gave 1-cyanonaphthalene (2·95 g., 99%), b. p. 83°/0·15 mm., m. p. 33—34°.

(*b*) For reactions of 1-bromo- or 1-iodo-naphthalene with cuprous cyanide in pyridine (Table 1), the solution (150 ml.) was added to concentrated aqueous ammonia and the product extracted with benzene. The extract, after washing with ammonia and 6N-hydrochloric acid, was analysed by gas chromatography; 1-methylnaphthalene was added as an internal standard.

(*c*) Reverse reaction was attempted between 1-cyanonaphthalene and cuprous bromide under similar conditions to those described in (*b*). Gas chromatography revealed no product other than unchanged cyanide (95% recovery).

(*d*) For rate measurements in 1-bromonaphthalene–cuprous cyanide systems (Table 4) the procedure was the same as that used for the halide-exchange reactions. Biphenyl was added to solutions, before reaction, to serve as an internal standard in gas chromatography, but more precise results were given by normalisation of the 1-bromo- and 1-cyano-naphthalene peaks. The instrument was less sensitive to the cyanide than to the bromide.

Reaction of 1-*Bromonaphthalene with Cuprous Thiophenoxide.*—(*a*) A solution of 1-bromonaphthalene (0·0125 mole) and cuprous thiophenoxide (0·125 mole) in pyridine (150 ml.) was refluxed for 24 hr., and the solution then cooled, added to concentrated aqueous ammonia, and the product extracted with benzene. The extract, after washing with aqueous ammonia, 6N-hydrochloric acid, and sodium chloride solution, was analysed by gas chromatography, with 1-methylnaphthalene and phenanthrene as internal standards; 1-phenylthionaphthalene (27%) and unchanged 1-bromonaphthalene (70%) were found.

(*b*) No reverse reaction was detected when a mixture of 1-phenylthionaphthalene and cuprous bromide was examined under conditions similar to those in (*a*).

(*c*) Thiophenol (0·01 mole) and cuprous oxide (0·005 mole) were stirred for 15 min. in dimethyl sulphoxide (25 ml.) at 50°; cuprous thiophenoxide appeared as a pale yellow solid. A solution of 1-bromonaphthalene (0·01 mole) in dimethyl sulphoxide (25 ml.), also containing phenanthrene as an internal standard, was added, and the temperature raised to 144°; the mixture remained heterogeneous. After 4 hr., extraction and analysis showed 1-phenylthionaphthalene (21%) and unchanged bromide (79%). Under similar conditions in dimethylformamide the yield was 31%.

(*d*) Reaction was repeated as in (*c*) except that the amount of thiophenol was raised to 0·02 mole and sodium hydroxide (0·01 mole) was also present. At 144° the mixture became homogeneous. Analysis showed 2·4% of 1-phenylthionaphthalene and 97% of unchanged bromide. Under similar conditions in dimethylformamide the yield was 3·8% and 96% of the bromide was unchanged.

Reaction of 1-*Bromonaphthalene with Cuprous Thiocyanate.*—A solution of 1-bromonaphthalene (0·0125 mole) and cuprous thiocyanate (0·125 mole) in pyridine (150 ml.) was refluxed for 24 hr. and the product isolated as described for the 1-phenylthio-derivative. Gas chromatography indicated that 73% of the bromide was unchanged and no product with b. p. $<\sim$360° was present. The infrared spectrum showed no peak due to the SCN group. Chromatography on alumina yielded 1-bromonaphthalene and a solid sulphur-containing fraction (0·2 g., ~10%), m. p. 105—140°, which was probably a mixture of sulphides.

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