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Kinetic and Product Studies on Ullmann Amination of 1-Halogenoanthraquinones catalysed by Copper(I) Salts in Acetonitrile Solution

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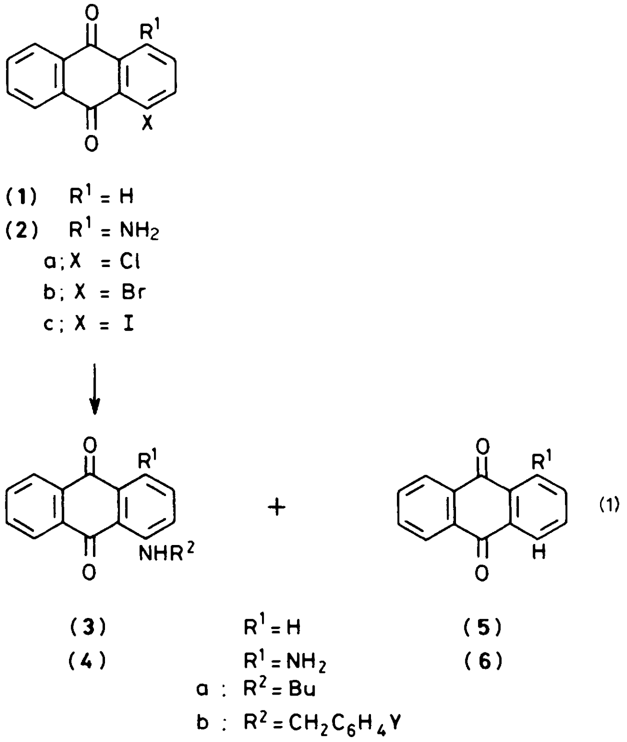
The kinetics and products of reactions of some primary amines (RNH_2) with 1-halogenoanthraquinones (AQX) promoted by copper salts, particularly tetrakis(acetonitrile)copper(I) tetrafluoroborate, have been investigated in acetonitrile solution at 70 °C. Provided that oxygen does not come into contact with solutions of the copper(I) salt and amine, the kinetics of the reaction have the simple form $v = k[AQX][RNH_2][Cu^I]$, and the products consist almost entirely of the aminated anthraquinone, AQNHR, and dehalogenated material, AQH, their ratio being directly proportional to $[RNH_2]$. The reaction rate is dependent on the identity of the departing halogen X, decreasing in the sequence I > Br > Cl, but the product ratio is little affected. *N*-Deuteriation of the reactant amine gives rise to a small kinetic isotope effect, but the product ratio is unaffected. Conversely deuteriation on the α-carbon atom of the amine has little kinetic effect but leads to a four-fold increase in the ratio of aminated to dehalogenated product. The observations are interpreted in terms of (i) formation of a copper(I)–amine complex, (ii) activation of this species for attack on AQX by proton abstraction from an amine ligand by a free molecule (stepwise or concerted), and (iii) generation of an arylcopper(III) intermediate which is partitioned between formation of AQNHR by attack of an external amine molecule and formation of AQH by an intramolecular process involving hydrogen transfer from the α-carbon atom in the amide ligand generated in (ii). Exposure of the initial copper(I)–amine complex to oxygen leads to a new complex, itself capable of reacting with AQX, which on prolonged incubation at 70 °C in the presence of an excess of amine is transformed back to its original state.

Ullmann amination of halogenoarenes, the replacement of halogen attached to aromatic nuclei by amines (or ammonia) in the presence of copper or its salts, is a reaction of considerable synthetic and commercial importance.[1] The reaction can be conducted under a bewildering variety of conditions and, partly for this reason, proposals concerning its mechanism have been numerous.[2] In particular there have been conflicting reports concerning the oxidation state of the copper responsible for the catalysis and of that incorporated in intermediates generated along the reaction pathway: copper-(I), -(II), and -(III) have all been invoked at various times and in various situations. Likewise, electron-transfer processes and the formation of free radicals have been invoked in discussing amination and related copper-assisted nucleophilic aromatic substitutions.

The present investigation was undertaken in the hope that light could be shed on the mechanism of a commercially important group of Ullmann aminations of halogenoanthraquinones. Industrially, the reaction is conducted in aqueous solution but it was felt that use of acetonitrile as solvent should simplify the redox situation as well as permitting the reaction to be studied under homogeneous conditions. A convenient system was found to be the reaction of n-butylamine or benzylamine with 1-halogenoanthraquinones (**1**) or with 1-amino-4-halogenoanthraquinones (**2**) in the presence of copper(I) or copper(II) tetrafluoroborate; most of the present results refer to this system. The kinetics of replacement of the halogen by amine and the competitive dehalogenation process (1) were examined. In conjunction with determination of kinetic isotope effects both from directly observable reaction rates and from product proportions, the results permit some conclusions to be reached about the mechanism of the reactions under these conditions.



Results

All reactions were carried out at 70 °C in dry acetonitrile under purified nitrogen. Typical reagent concentrations were: halogenoanthraquinone 2mM, amine 0.25—2M. The copper salt was normally tetrakis(acetonitrile)copper(I) tetrafluoroborate at a concentration in the range 1—5mM. Use of the perchlorate instead of the tetrafluoroborate brought about no detectable change in behaviour. Product analysis was performed by h.p.l.c.,

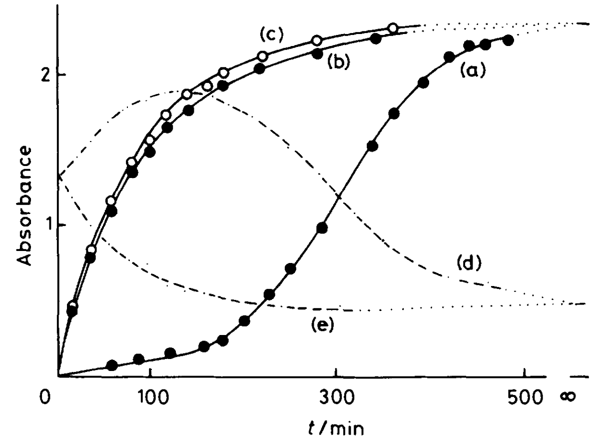


Figure 1. Absorbance–time curves for the reaction of (**2b**) (2mM) with butylamine (0.95M) in the presence of $[(MeCN)_4Cu]^+BF_4^-$ (3.8mM) in acetonitrile at 70 °C. Solid lines refer to $\lambda = 618$ nm (**6a**) and broken lines to $\lambda = 475$ nm [absorbance maximum of (**2b**)]. Pre-treatment of reactants: (a) and (d), Method A; (b) and (e), Method B; (c), Method C

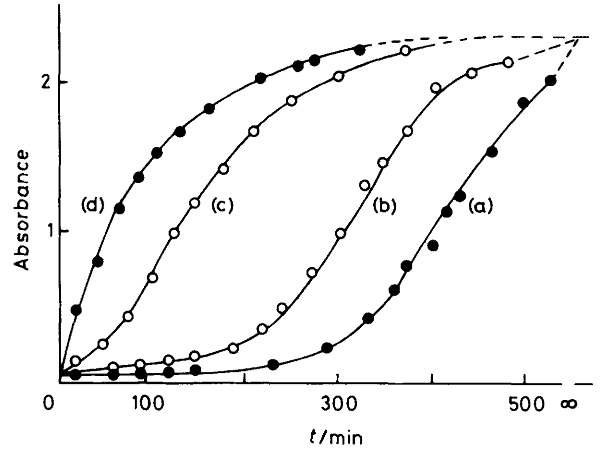


Figure 2. Changes in absorbance at 618 nm of reaction mixtures prepared by Method A containing (**2b**) (2mM), butylamine, (0.95M), and $[(MeCN)_4Cu]^+BF_4^-$ (3.8mM) in acetonitrile at 70 °C. Incubation periods at 70 °C were (a) 2 min; (b) 5 min; (c) 20 min; (d) 120 min

which showed that 96—98% of starting material was converted into a mixture of (**3**) + (**5**) or (**4**) + (**6**). Of the residual material, the major component was the 1-hydroxyanthraquinone. The aminated compounds (**3**) and (**4**) were the major products, and these could be readily monitored spectrophotometrically, *e.g.* at 475 nm for (**3**) and 618 nm for (**4**), wavelengths much longer than those at which the corresponding halogenoanthraquinones absorb. No reaction was found to occur in the absence of the copper salt. Atmospheric oxygen inhibited the reaction and exposure of solutions in which reactions had been carried out under nitrogen to atmospheric oxygen led to complete degradation of the aminated product within a few minutes.

Two kinetic procedures were used, one in which reaction mixtures were sampled at intervals, and the samples quenched in 2% aqueous ammonia and analysed by h.p.l.c., and the other in which the formation of the aminated product was monitored spectrophotometrically *in situ* by use of a previously described[3] two-limbed reaction vessel incorporating an optical cell. By following reactions by both methods it was found that the residual reactant concentration at any time *t* was proportional to $A_\infty - A_t$, where *A* is the absorbance of the solution at the wavelength of maximum absorption of the aminated product. This observation permits the inference that the relative proportions of aminated product (**3**) or (**5**) and dehalogenated product (**4**) or (**6**) remain constant throughout the reaction, and that this arises because the pathways to them are of the same kinetic order with respect to halogenoanthraquinones and copper salt. The large excess of amine normally used prevents the extension of this inference to the third reactant. Because of its convenience, the spectrophotometric procedure was used in most experiments.

Pre-treatment of the Reactants.—Reactions were initiated by mixing of acetonitrile solutions of the reagents which had previously been freed of dissolved oxygen by freeze–pump–thaw cycles and then brought to the reaction temperature. Different kinetic behaviour was observed, however, depending on whether the copper(I) salt was mixed with the amine or with the anthraquinone prior to deoxygenation, such combinations being required with the two-limbed reaction vessel. When the copper(I) salt was mixed with butylamine before removal of oxygen (method A), there was a lengthy induction period after the admixture of the halogenoanthraquinone before aminated product began to appear [Figure 1(a)]. This induction period was, however, shorter than when an equivalent concentration of copper(II) tetrafluoroborate was used.[*] It could be shortened somewhat by use of higher amine or copper(I) concentration, but was found to be most effectively shortened simply by maintaining the copper(I) salt and amine solution at 70 °C for an extended period before adding the halogenoanthraquinone solution. After a 2 h incubation (method B) no induction period was observed (Figure 2) and the behaviour was then identical [see Figure 1(b) and (c)] with that observed when the amine solution was deoxygenated separately from the copper(I) solution and the reactants were mixed immediately after they had been brought to 70 °C (method C). Under all conditions, however, the yield of aminated product was the same and varied only with the concentration of amine.

Table 1. Products of quenching reaction mixtures prepared by method A[a]

Quenching medium	Products (%)				
	(**2b**)	(**3a**)	(**6**)	(**7**)	Unknown
NH_3–H_2O	5.4	10.8	82.5	N.d.	1.3
	6.3	8.9	82.4	N.d.	2.4
H_3O^+–H_2O	7.8	7.8	6.2	77.3	0.9
	6.4	8.2	7.8	76.8	0.9

[a] Initial concentrations: (**2b**) 1.98mM; $[(MeCN)_4Cu]^+ClO_4^-$ 2.3mM; butylamine 0.95M. N.d. = not determined.

It was further observed that, when reaction mixtures were prepared using method A, the absorbance at 475 nm, at which (**2b**) has it long-wavelength maximum, increased to a maximum, at which time formation of aminated product (**4a**) was at its most rapid, and then decreased [Figure 1(d)]. Quenching a reaction mixture at the time of maximum absorbance at 475 nm by pouring it into deoxygenated aqueous 2% ammonia or aqueous 2% acid gave the results detailed in Table 1. The phenolic quinone (**7**) was the major product (> 80%) when water was used, but the dehalogenation product (**6**) was found in roughly equivalent amount after the acid quench.

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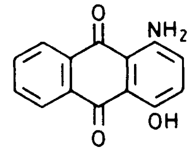
[*] Use of copper(II) tetrafluoroborate in place of the copper(I) salt had no effect on the product ratio on completion of the reaction.



(7)

Reaction Kinetics and Products.—Methods B and C gave identical results, the rate of disappearance of the halogenoanthraquinone showing a first-order concentration dependence in the presence of a large excess of amine. First-order rate coefficients (k_{obs}) were evaluated by a least-squares program from absorbance–time data on duplicate runs. Correlation coefficients were greater than 0.99 over 2—3 half-lives, and rate coefficients were reproducible usually within $\pm 5\%$. All values of k_{obs} and of the ratio of aminated to dehalogenated products reported in the Tables are mean values from duplicate experiments.

Table 2 gives the rate and product results for 1-amino-4-bromoanthraquinone (**2b**). It is evident that the results fit the kinetic equation $-d[(\mathbf{2b})]/dt = k_{obs}[(\mathbf{2b})] = k_3[(\mathbf{2b})][RNH_2][Cu^I]$. There is a modest rate variation among the four primary alkylamines used. Aniline reacts at about one thirtieth of the speed of benzylamine and at less than one hundredth of the speed of butylamine. t-Butylamine (0.95M) showed no reaction over 48 h in the presence of the copper(I) salt under the same conditions, and 1-methylheptylamine behaved similarly. The effects on the reaction rates and substitution–dehalogenation ratio of various 4-substituents in benzylamine are shown in Table 3; a 4—5-fold increase in rate is observed as the substituent is changed from Cl to OMe, and the results show a fair fit to the simple Hammett equation with $\rho = 1.362$ ($r = 0.993$). The product ratios do no show a linear correlation with σ.

The effect of changing the departing halogen is shown in Table 4 using the 1-halogenoanthraquinones (**1a**—**c**). An approximately eight-fold rate variation is observed in the sequence I > Br > Cl. A larger difference in reactivity is observed for (**2a**) and (**2b**) (Table 2) than for (**1a**) and (**1b**). The order of halogen reactivity is the reverse of that observed in nucleophilic aromatic substitutions not assisted by copper. The substitution–dehalogenation product ratio is much less affected than the overall reaction rate by the change in leaving group. Almost no change in reactivity or product ratio results from methylation of the amino-group in (**2b**) (Table 5).

Isotope Effects.—In order to trace the origin of the hydrogen atom which replaces halogen in the dehalogenated product, a series of experiments was undertaken using *N*,*N*-dideuteriated n-butylamine and benzylamine and using α,α-dideuteriated benzylamine. Kinetic results and product ratios are in Table 6, from which it can be seen that a small kinetic isotope effect (1.35 at 70 °C) was observable with both *N*-deuteriated amines, but α-deuteration had no kinetic effect. However, α-deuteration had a marked effect on the product proportions, indicating that the dehalogenated product derives its hydrogen from those attached to the benzylic carbon atom. The presence of deuterium in the product was confirmed mass spectrometrically (> 90% $C_{14}H_8DNO_2$) and by ^{13}C n.m.r. spectroscopy (signal at

Table 2. Effect of variation in reactant concentration on k_{obs} for (**2b**)[a]

$[RNH_2]$/M	$[Cu^I]$/mM	Method	10^3k_{obs}/min^{-1}	[(**4**)]/[(**6**)]
(a) n-Butylamine				
0.250	2.30	B	1.90	0.62
0.475	4.60	B	7.15	0.90
0.95	4.60	B	15.6	2.39
	3.80	B	11.3 (11.2)[b]	2.42 (2.41)[b]
	3.80	C	12.2[c] (12.3)[b]	2.39[c] (2.37)[b]
	3.80	C	0.7[d]	1.80[d,e]
	1.96	B	5.9 (6.1)[b]	2.35 (2.38)[b]
	1.15	B	4.0	2.32
1.90	4.60	B	28.6	4.48
(b) Benzylamine				
0.475	3.80	B	1.35	0.89
	3.80	C	1.40	0.88
0.95	3.80	B	2.70	2.32
	3.80	C	3.10	2.17
1.90	3.80	B	6.0	4.26
	3.80	C	6.1	4.26
(c) s-Octylamine				
0.475	3.80	C	6.5	1.34
0.95	3.80	C	13.8	2.49
1.90	3.80	C	26.8	4.97
(d) 4-Phenylbutylamine				
0.95	3.80	C	9.9	2.37
1.90	3.80	C	17.7	4.67
(e) Aniline				
0.95	3.80	C	0.10	2.00

[a] [(**2b**)] = 1.95mM throughout. [b] Reaction followed by sampling and h.p.l.c. analysis for (**2b**). [c] Mean of seven determinations with reactant solutions maintained at 70 °C for times from 2 to 120 min. [d] Reactant (**2a**). [e] Product ratio after one half-life.

Table 3. Effects of 4-substituents in benzylamine on the rate and products of reaction of (**2b**)[a]

Substituent	10^3k_{obs}/min^{-1}	[(**4b**)]/[(**6**)]
OMe	6.3	3.38
Me	5.7	3.20
H	2.9	2.36
Cl	1.45	2.37

[a] Method C. Initial concentrations: (**2b**) 1.95mM; $[(MeCN)_4Cu]^+BF_4^-$ 4.6mM; $ArCH_2NH_2$ 0.95M

Table 4. Effect of halogen variation on the reaction of (**1**) with n-butylamine[a]

X	Method	n[c]	10^3k_{obs}/min^{-1}	[(**3**)]/[(**5**)]
Cl	B	2	3.3	2.12
	C	4	3.3	2.14
Br	B	2	7.6 (7.4)[b]	2.57 (2.62)[b]
	C	4	7.7	2.41
I	B	2	25.8	2.43
	C	4	26.0	2.47

[a] Initial concentrations: (**1**) 1.95mM; $[(MeCN)_4Cu]^+BF_4^-$ 4.6mM; n-butylamine 0.95M. [b] Initial concentration of (**1**) 0.98mM. [c] Replicate number of experiments.

Table 5. Kinetic and product ratio effects of *N*-methylation of (**2b**)[a]

R′	n	10^3k_{obs}/min^{-1}	[(**4**)]/[(**6**)]
NH_2 (**2b**)	2	12.2	2.36
NHMe	4	11.7	2.39
NMe_2	4	11.7	2.35

[a] Method C. Initial concentrations: (**2b**) 1.95mM; $[(MeCN)_4Cu]^+BF_4^-$ 3.8mM; n-butylamine 0.95M

Table 6. Kinetic and product isotope effects on the reaction of (**2b**) with n-butylamine and benzylamine[a]

Amine	10^3k_{obs}/ min^{-1}	k_{obs}^H/k_{obs}^D	[(**4**)]/[(**6**)]	D/H
$C_4H_9NH_2$	15.9		2.37	
$C_4H_9ND_2$	11.8	1.35	2.36	1.0
$C_6H_5CH_2NH_2$	2.90		2.27	
$C_6H_5CH_2ND_2$	2.15	1.35	2.29	1.01
$C_6D_5CD_2NH_2$	2.90	1.00	9.00	3.96

[a] Method C. Initial concentrations: (**2b**) 1.95mM; $[(MeCN)_4Cu]^+BF_4^-$ 4.61mM; amine

117 p.p.m. in the spectrum of 1-aminoanthraquinone appeared as a weak 1:1:1 triplet).

Discussion

In what follows, our discussion will concern reactions in solutions prepared by methods B and C. Discussion of the behaviour of reaction mixtures prepared by method A will be deferred until the end.

Copper(I) *Complexes in Acetonitrile Solution.*—Solutions of copper(I) salts in acetonitrile were prepared by treatment of the corresponding copper(II) salt with metallic copper according to a literature procedure.[4] It is known that the copper(I) ion carries four tetrahedrally disposed acetonitrile molecules as ligands and is thermodynamically stable relative to the copper(II) salt. Acetonitrile is, however, a fairly weak ligand and in the presence of amines is displaced. There is ^{63}Cu n.m.r. evidence[5] that quite low concentrations of pyridine convert $[(MeCN)_4Cu]^+$ into $[(C_5H_5N)_4Cu]^+$, and the primary amines, being more powerful σ-donors, albeit without π-acceptor properties, should be no less capable of displacing acetonitrile as a ligand. We were unable to detect ^{63}Cu signals from such solutions, however, and, while this negative evidence could be taken to indicate a complex of lower symmetry than that formed with pyridine, other factors unrelated to structure might be responsible. In what follows we shall assume that the complex present initially in solutions prepared by method C or after incubation for 120 min at 70 °C (method B) is $[(RNH_2)_4Cu]^+$, although our conclusions would be little different if the ligand-to-copper ratio were 2:1.

The Stepwise Nature of the Reaction.—Two lines of reasoning lead us to infer that the reaction takes place in stages, one of which is rate-limiting, with a later stage determining the product proportions by partitioning of an intermediate (X). First we observe that changing the departing halogen markedly affects the rate of reaction under specified reaction conditions but has only a small effect on the product proportions. This is typical evidence for rate-limiting formation of a reactive intermediate which is rapidly transformed to products along competing pathways. The constancy of the ratio of aminated to dehalogenated product throughout the course of reaction and its invariance with halogenoanthraquinone and copper(I) concentration, the latter parameter influencing the observed reaction rate, are also consistent with this interpretation. Particularly strong evidence for partitioning of an intermediate formed in the rate-determining step is provided by the results obtained with *N*- and *C*-deuteriated amines: *N*-deuteriation changes the reaction rate without affecting the product proportions while use of α-deuteriated benzylamine leads to no kinetic effect but a four-fold increase in the ratio of aminated to dehalogenated product.

The Role of the Amine.—As well as the presumed complexation of Cu^I occurring immediately on mixing acetonitrile solutions of $[(MeCN)_4Cu]^+BF_4^-$ and amine, the amine is involved in two further ways in the reaction. A further *free* amine molecule is involved in the rate-determining step of the reaction and a second one is responsible for conversion of the intermediate complex (X) generated in the rate-determining step into the aminated product. The latter conclusion rests on the proportionality between the product ratio [(**4**)]/[(**6**)] and $[RNH_2]$ (Table 2).

The role of the free amine in the rate-determining step is plausibly related to its basicity rather than its nucleophilic properties towards the carbon–halogen bond. While *N*-deuteriation leads to a kinetic isotope effect, this is rather small. It could conceivably be either a primary effect (with associated secondary isotope effects arising from the considerable number of N–D bonds not actually broken in the reaction) or a composite of a pre-equilibrium isotope effect with a rate-limiting step not involving N–H breaking but with secondary isotope effects (2). In the former case the transition state would

$$L_nCu\text{-}NH_2R^+ + RNH_2 \rightleftharpoons L_nCu\text{-}NHR + RNH_3^+ \quad (2a)$$

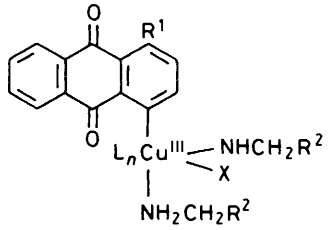
$$L_nCu\text{-}NHR + (\mathbf{1})\text{ or }(\mathbf{2}) \longrightarrow X \quad (2b)$$

necessarily consist of the copper complex, amine, and halogenoanthraquinone. Distinction between these two possibilities does not seem possible on the present evidence and existing knowledge of isotope effects in base-catalysed reactions.[6] We note, however, that the solvent isotope effect on the hydrolysis of phenyl acetate catalysed by methylamine acting as a general base in aqueous solution is only 1.7 at 5 °C.[7] For the mechanism in (2), we might anticipate a rather small equilibrium isotope effect on (2a) and only secondary isotope effects on (2b) provided that this slow step were nucleophilic attack on the halogenoanthraquinone by the metal (or oxidative addition of the halogenoanthraquinone to the metal[8]).

Finally, the ratio of aminated to dehalogenated products is directly proportional to the concentration of free amine in the reaction mixture. The simplest interpretation of this in the light of the foregoing discussion is that an intermediate is partitioned between reaction with a free amine molecule to give the aminated product and reaction with an amine molecule which is not free but rather is acting as a ligand to copper in the intermediate. Partitioning then represents the competition between an intermolecular amination and intramolecular hydrogen transfer. Any formulation of the competitive processes in which the kinetic order in amine of the amination pathway exceeds that of the dehalogenation pathway by one would be consistent with our observations, but we believe our proposal to be the simplest.

The Nature of the Partitioned Intermediate (X).—Overall, Ullmann amination is an aromatic nucleophilic substitution. The sequence of reactivities I > Br > Cl is, however, the reverse of that normally associated with intermediate formation of an adduct of the Meisenheimer-type from, for example, nitro-activated halogenoaromatics. Moreover, the observation that the product ratio is almost independent of the leaving group suggests that the carbon–halogen bond is already cleaved in the intermediate. The intermediate is evidently susceptible to rapid attack by nucleophilic amines as well as undergoing an apparent intramolecular hydrogen transfer from the C–H bonds of amines bound into the intermediate.

We believe that the intermediate is best and most plausibly formulated as an arylcopper(III) complex bearing one or more amine ligands and one amide ligand (**8**). Our reasons are as follows. A copper(III) derivative would result from oxidative



(8)

addition of the halogenoaromatic to a copper(I) complex. Secondly, copper(III) complexes are normally stabilised by hard ligands such as O^{2-} or F^-. The amide ligand resulting from proton abstraction by the amine from an amine molecule acting as a ligand for copper(I) in the reacting complex [equation (2a)] could provide the necessary stabilisation in the present case just as has been suggested for copper–albumin complexes.[9] Thirdly, such a complex would be sufficiently electrophilic to be attacked by external nucleophiles. Finally, intramolecular hydride transfer from the C–H bonds of the amide ligand, for which there are, however, to the best of our knowledge, no precedents,[10] can be readily envisaged to give rise to the dehalogenated product together with re-formed copper(I) complex and a molecule of imine, $R^2CH{=}NH$.

Detection of such an imine, which would be difficult at the concentration levels expected in these reactions, was not attempted. Reaction mixtures showed no detectable e.s.r. signals which might have been attributable to copper(II) or copper(III) species, but copper(III) complexes, although formally of a d^8 metal, are not all e.s.r.-active[11] and, if active, might not be detectable at room temperature.

We add that we are not the first to advocate the formulation of intermediates in Ullmann reactions as copper(III) complexes. Cohen *et al.*[12] have invoked such species in conjunction with copper(I) complexes in halogen-exchange reactions of 2-iodo-*N*,*N*-dimethylbenzamide but contrary views have been expressed.[13] Oxidative addition of organic halides to low-valent metal complexes is widely seen as an important step in reactions related to Ullmann's.[14] In the halogenoanthraquinones, Hida and his co-workers have examined copper-assisted reactions in protic solvent mixtures using aliphatic amines, diamines, and amino alcohols.[15] While concluding that the important catalytic species is a copper(I) complex, they have focussed attention on electron-transfer processes and the additional catalytic role of copper(II) when present with copper(I) salts in some,[15b,c] although not all,[15e] systems. They seem, however, to have stopped short of suggesting the involvement of organocopper(III) species.

Reactions in Solutions Prepared by Method A.—The results suggest that exposure of $[(MeCN)_4Cu]^+BF_4^-$ and amines in acetonitrile solution to oxygen, followed by removal of the excess of oxygen (Method A), leads to the formation of a complex which is not a simple copper(II)–amine complex. It is converted on incubation at 70 °C into a complex indistinguishable, in its kinetic and product-forming behaviour with halogenoanthraquinones, from the complex formed directly from $[(MeCN)_4Cu]^+BF_4^-$ and an excess of amine. In the presence of halogenoanthraquinone it gives rise over 2 h or so at 70 °C to a metastable intermediate which can be quenched. In competition with this reaction, it presumably undergoes thermal transformation, and the observed products (Table 1) result from reaction of the halogenoanthraquinone with both complexes to some extent. Both pathways appear to lead to the same organocopper(III) complex, which is partitioned between amination and dehalogenation as already described.

Present evidence does not permit us to say much about the complex formed initially in reaction mixtures made up by Method A. Solutions in acetonitrile are certainly coloured, blue at room temperature, becoming green reversibly on cooling. Attempts to isolate a crystalline material for further examination using Method C were not successful, although some colourless, very oxygen-sensitive solid was obtained on some occasions by careful removal of volatile material from acetonitrile–pentane solutions, but this rapidly turned blue even before exposure to the air. There have been numerous reports in recent years of the characterisation of copper(I) halide–amine complexes and their reactions with molecular oxygen in aprotic solvents.[16] The product complexes, usually containing two copper atoms,[17] are often active oxidation catalysts for organic reactions such as phenolic coupling. In the present instance, the number of copper atoms involved is not known, but in the absence, initially, of halide ions, multi-atom complexes do not seem very likely.

Conclusion.—The reaction system used in the present investigation has proved to be a particularly straightforward one to study and has led to a rather simple interpretation. In this, proton abstraction from a copper(I)–amine complex leads to enhanced reactivity towards the carbon–halogen bond of 1-halogenoanthraquinones and formation of an organocopper(III) intermediate. Partitioning of this species between intramolecular hydrogen transfer (which can be formulated as a hydride-transfer process or as an extended reductive elimination) and attack by an external amine molecule gives rise to the two major reaction products. We have found no evidence for electron-transfer processes leading to organic free radicals or to copper(II) species provided oxygen is rigorously excluded from contact with the copper(I)–amine complex. In the light of the diversity of reaction systems that have been used for Ullmann-type reactions over the past 80 years and the complexity of the pattern of observations that has been reported we remain cautious about claiming generality for our interpretation in the present instance.

Experimental

Materials.—Acetonitrile (Fluka, puriss, p.a.) after storage over P_2O_5 was distilled and stored over type 3A molecular sieves. Amines were doubly distilled from KOH pellets and stored over molecular sieves.

Tetrakis(acetonitrile)copper(I) perchlorate was prepared from copper(II) perchlorate by refluxing with an excess of copper turnings in dry acetonitrile until the solution was colourless.[4] Filtration and cooling yielded the crystalline salt. The corresponding tetrafluoroborate was prepared from copper(I) oxide by treatment with hot tetrafluoroboric acid and acetonitrile. Crystallisation occurred on cooling under nitrogen and the crystals were washed with diethyl ether–acetone (80:20). All manipulations of the copper(I) salts were carried out under nitrogen.

Reactants and authentic specimens of products were either commercial samples purified by column chromatography and recrystallisation, or synthesised by literature methods, or (in the case of aminated products) isolated chromatographically from relatively large-scale Ullmann reactions under kinetic conditions. They are listed in Table 7.

Deuteriated Amines.—*N*,*N*-Dideuterio-butylamine and -benzylamine were prepared by five-fold exchange of the amine in dry ether with D_2O followed by drying and distillation from potassium. α,α,2,3,4,5,6-Heptadeuteriobenzylamine was prepared from perdeuteriotoluene by bromination (*N*-bromosuccinimide in CCl_4) followed by treatment of the distilled

Table 7. Origin and m.p.s of reactants and products

Substituents in AQ			M.p. (°C)		
1-	4-	Origin[a]	Obs.[b]	Lit.	Ref.
NH_2		C	252	253—254	18
NHMe		S	169	170	19
NHBu		I[c]	80	81—82	19
NHPh			146	147.5	20
NMe_2		S	179	180	21
Cl		C[c]	164	162	22
Br		S[c]	187	188	23
I		S[c]	206	204.5	23b
NH_2	NHBu	I[c]	140	142	15b
NH_2	NHOctyl	I[c]	112	114	24
NH_2	$NHCH_2Ph$	I[c]	168	167	24
NH_2	Cl	C	261	263	25
NH_2	Br	C[c]	170	170—176 178.5—179.2	26 15b
NHMe	NHBu	I	182	*d*	27
	Br	S	194	195—196	28
NMe_2	NHBu	I	152		27[e]
	Br	S	176	178	29

[a] C = commerical sample; I = Isolated from Ullmann reactions; S = synthesised. [b] Uncorrected. [c] Purity confirmed by elemental analysis. [d] Absorption spectrum agrees with literature. [e] Homogeneous by t.l.c.; absorption spectrum ($\lambda_{max.}$/nm) 624 (ε 18 000) and 586 (15 000) in ethanol.

heptadeuteriobenzyl bromide with potassium phthalimide in dimethylformanide, and hydrolysis. The ^1H n.m.r. spectrum of the product indicated essentially complete deuteriation of the α-positions.

Kinetic Measurements.—The progress of reactions was usually followed spectrophotometrically (Pye-Unicam SP 8-100) by the appearance of the aminated product. A two-limbed reaction vessel incorporating an optical cell of 1 mm pathlength was used[3] and this was held in a thermostatted cell block throughout the faster reactions, but for slower reactions was transferred to it periodically from an external thermostat. The method was checked by carrying out reactions in a series of small Warburg tubes which, after the reactants had been mixed, were removed from the thermostat at timed intervals, cooled, and analysed for unchanged halogenoanthraquinone and aminated product by h.p.l.c.

Reaction vessels and solutions were freed from oxygen prior to mixing of the reagents by three successive freeze–pump–thaw cycles and finally sealed under nitrogen and brought to 70 °C. After a period of incubation at 70 °C the reactants were mixed. Three variants of this general procedure were adopted, differing in the division of the reactants, 1-halogenoanthraquinone, amine, and copper catalyst, between the two limbs of the reaction vessels before and during deoxygenation and in the length of the incubation period at 70 °C prior to mixing: *Method A:* limb 1, copper salt + amine; limb 2, halogenoanthraquinone; incubation period 2 min; *Method B:* reactants separated as in Method A; incubation period 120 min; *Method C:* limb 1, amine; limb 2, copper salt + halogenoanthraquinone; incubation period 2 min.

First-order rate coefficients were derived from the analytical or absorbance figures obtained usually over two half-lives of the reaction by use of a least-squares program. All experiments were carried out in duplicate and gave rate coefficients reproducible usually within ±5% of the mean.

H.p.l.c. Analyses.—These were carried out on a Water's 440 liquid chromatograph with Hewlett Packard HP 3390A integrator. The column used was normally Hi-Chrom RP10, although in some cases where higher resolution was needed, a Hi-Chrom RP18-2776 column was used. The solvent was 70:30 H_2O–CH_3CN. The copper catalyst was removed from reaction mixtures by dilution with ether and extraction with dilute aqueous ammonia, or more simply by passing the reaction mixture through a silica gel plug. U.v. detector responses were calibrated against solutions of authentic samples of known concentration and the calibration was checked periodically by the use of internal standards, 1-iodoanthraquinone for reactions involving chloro- or bromo-anthraquinones and 1-amino-4-bromoanthraquinone for reactions of 1-iodoanthraquinone.

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