The Ullmann Condensation Reaction of Haloanthraquinone Derivatives with Amines in Aprotic Solvents. IV. Kinetic Studies of the Condensation with Ethylenediamine

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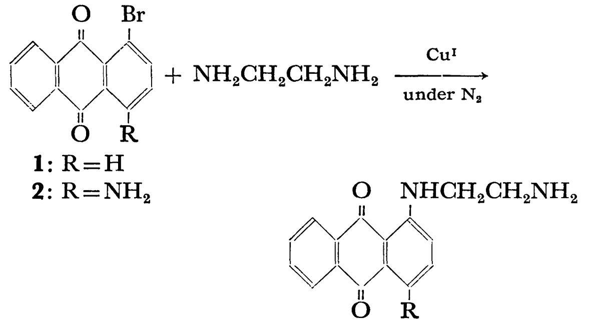
In the Ullmann condensation of bromoanthraquinones (AQBr) with ethylenediamine using copper(I) bromide as a catalyst, the reaction rate decreased with time which has been interpreted in terms of the formation of the ineffective copper(II) species. The kinetic investigation showed the reaction rate to be first order both for the copper(I) species and AQBr. After prolonged reaction the copper(I) species was quantitatively converted to the copper(II) species, the copper(II) species appearing to have little catalytic activity due to strong coordination with ethylenediamine. The reactivities of the haloanthraquinones were dependent on the ease of coordination with Cu(I) and the rate of Cu(II) formation. The mechanism, including the reaction between Cu^I(AQBr) and ethylenediamine, has been proposed and discussed.

Aryl halides readily undergo nucleophilic replacement of the halogen atom by moieties such as OR and NH_2, with the aid of a copper catalyst. The reaction mechanism, has however, been the subject of little research and the catalytic action of the copper species remains obscure.

The authors have reported the mechanism of the Ullmann condensation reaction for haloanthraquinones with amines using copper salts as the catalyst in protic and aprotic solvents.[1–4] In aprotic solvents, the effective copper(I) species oxidizes to the ineffective copper(II) species during the course of reaction and the formation of the copper(II) species has been shown to have an important role in the reaction.[2,3] Thus, in the condensation with 2-aminoethanol, the resulting copper(II) species increased the catalytic activity of the copper(I) species. The pseudo-first order rate constant may be expressed as follows:

$$k = k_1[\mathrm{Cu^I}] + k_2[\mathrm{Cu^I}][\mathrm{Cu^{II}}].^{4)}$$

In this paper the reaction of haloanthraquinones with ethylenediamine, will be reported which is more reactive than 2-aminoethanol, by copper(I) catalyst in aprotic media.



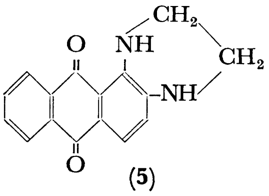
1: R=H
2: R=NH_2

3: R=H
4: R=NH_2

Experimental

General. 1-Bromoanthraquinone (**1**), 1-amino-4-bromoanthraquinone (**2**), and copper(I) bromide were prepared by the methods described in a previous paper.[2] Commercially available ethylenediamine was dried over sodium, distilled, and stored under nitrogen. The solvents used were dried by standard procedures, distilled, and stored under nitrogen. The details of the kinetic measurements have been described in Part I of this series.[2] The anthraquinone and 1-aminoanthraquinone formed in the course of reaction were analyzed by high speed liquid chromatography in a manner similar to that described in a preceding paper[4]: column, Zorbax ODS 25 cm; mobile phase, methanol–water 67: 33; temperature, 40 °C; detector, UV-254 nm. ESR spectra were measured as described in preceding papers.[3,4] IR and UV and visible spectra were recorded with JASCO IRA-1 and Shimadzu UV-200 spectrophotometers respectively. NMR spectra were obtained on a Hitachi R-24 spectrometer for solutions in dimethyl-d_6 sulfoxide with tetramethylsilane as an internal reference. Mass spectra were taken on a JEOL JMS-D 100 mass spectrometer by direct insertion.

Condensation Products. The condensation product, 1-(2-aminoethylamino)anthraquinone (**3**), was very liable, cyclizing thermally to give compound (**5**).[5] The condensation reaction of **1** and **2** with ethylenediamine in 1,2-dimethoxyethane–methyl cellosolve (4: 1) solution were conducted at temperatures below 100 °C in order to avoid possible side reactions, *e.g.*, cyclization of the condensation products.



(**5**)

The condensation products were obtained from the reaction mixture in a following manner: The solvents were removed under reduced pressure and the reaction mixture poured into water. After filtration, the products were washed with water and dried and the precipitate chromatographed on a silica gel column with benzene–methanol (4: 1, v/v) as the eluent. No formation of ring closed compounds were observed.

1-(2-Aminoethylamino)anthraquinone (3): $\lambda_{max}(C_2H_5OH)$ 501 nm (ε 6460); IR (KBr) 1660 cm^{-1} (C=O); NMR δ=2.37 (2H, disappearing on deuteration, NH_2), 2.85 (2H, $-CH_2-$), 3.25 (2H, $-CH_2-$), 6.95—8.35 (7H, quinone ring), 9.80 (1H, NH); MS, *m/e*=266 (M^+).

1-Amino-4-(2-aminoethylamino)anthraquinone (4): $\lambda_{max}(C_2H_5OH)$ 501 nm (ε 15700), 571 nm (ε 14100); NMR δ=2.85 (2H, $-CH_2-$), 3.44 (2H, $-CH_2-$), 7.10—8.40 (6H, quinone ring), 10.91 (1H, disappearing on deuteration, NH); MS, *m/e*=281 (M^+).

Results and Discussion

The reactivities of the haloanthraquinones in the presence or absence of copper(I) catalyst have been compared in Fig. 1 and indicate the following observations:

(i) The copper(I) catalyst greatly enhanced the reactivities of the haloanthraquinones.

(ii) 1-Bromoanthraquinone (**1**) was more reactive than 1-amino-4-bromoanthraquinone (**2**), both in the absence and presence of catalyst. The relative initial rates have been calculated as follows: **1** (without catalyst): **2** (without catalyst): **1** (with catalyst): **2** (with catalyst) = 20: 1: 5900: 5500.

(iii) The catalytic activity decreased as the reaction proceeded, a tendency more marked in reaction **2** than in **1**.

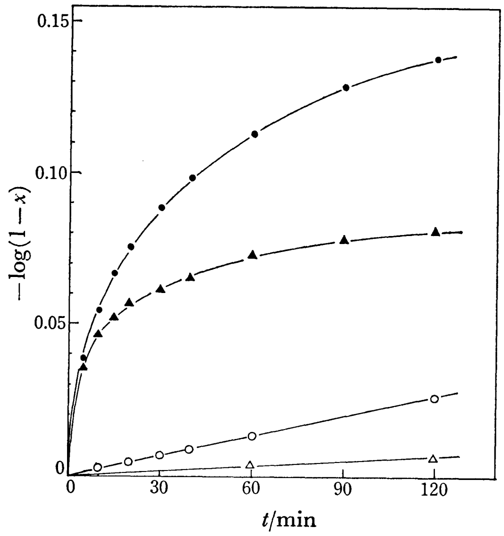


Fig. 1. Pseudo-first order plots of the reaction between bromoanthraquinones and ethylenediamine. $[\mathrm{AQBr}]_0 = 5\times10^{-3}$ mol/l, $[\mathrm{EN}]_0=0.5$ mol/l, $[\mathrm{CuBr}]_0=1\times10^{-3}$ mol/l, temp 70 °C, solvent 1,2-dimethoxyethane–methyl cellosolve 4: 1.
●: 1-BrAQ(**1**)–EN–CuBr, ▲: 1-NH_2-4-BrAQ(**2**)–EN–CuBr, ○: 1-BrAQ–EN, △: 1-NH_2-4-BrAQ–EN.

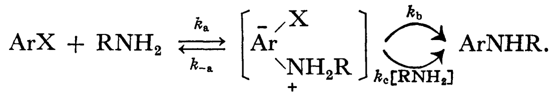
The above results may be explained in terms of the change in catalyst from copper(I) to copper(II). The following kinetic studies of the reaction between the haloanthraquinones and ethylenediamine reasonably support this reasoning.

Kinetics of Catalyst-free Reactions. Figure 1 shows that both the reactions of **1** and **2** in the absence of copper(I) bromide catalyst can be interpreted in terms of pseudo-first order kinetics. Since ethylenediamine (EN) was in a large excess, the second order rate constants were obtained by dividing the pseudo-first order rate constants by the concentration of amine. The second order rate constants of **1** and **2** (k_I and k_II) are expressed by Eqs. 1 and 2:

$$k_\mathrm{I}\ (\mathrm{l\cdot mol^{-1}\cdot min^{-1}}) = (3.2[\mathrm{EN}]+7.0)\times10^{-4}, \qquad (1)$$

$$k_\mathrm{II}\ (\mathrm{l\cdot mol^{-1}\cdot min^{-1}}) = (7.16\pm1.22)\times10^{-5}. \qquad (2)$$

Bunnett *et al.* reported that the nucleophilic substitution reactions of halonitrobenzenes with amines were accelerated, strongly or mildly with an increase in the concentration of amine or by the addition of bases.[6] Under these conditions the second order rate constant largely conform to Eq. 1. This observation has been interpreted by the following scheme:



$$\mathrm{ArX} + \mathrm{RNH_2} \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} \left[\overset{-}{\mathrm{Ar}}\begin{matrix}\diagup \mathrm{X}\\ \diagdown \underset{+}{\mathrm{N}}\mathrm{H_2R}\end{matrix}\right] \xrightarrow[k_c[\mathrm{RNH_2}]]{k_b} \mathrm{ArNHR}. \qquad (3)$$

Application of steady state hypothesis to this mechanism gives a second order rate constant (k') expressed by

$$k' = \frac{k_a k_b}{k_{-a}+k_b+k_c[\mathrm{RNH_2}]} + \frac{k_a k_c[\mathrm{RNH_2}]}{k_{-a}+k_b+k_c[\mathrm{RNH_2}]}. \qquad (4)$$

Assuming k_{-a} is much larger than $(k_b+k_c[\mathrm{RNH_2}])$ in the reaction of **1**, k_I may be expressed as follows:

$$k_\mathrm{I} = \frac{k_a k_b}{k_{-a}} + \frac{k_a k_c[\mathrm{RNH_2}]}{k_{-a}}. \qquad (5)$$

By comparing Eq. 5 with Eq. 1, $k_a k_b/k_{-a}$ and $k_a k_c/k_{-a}$ have been evaluated as $7.0\times10^{-4}\ \mathrm{l\cdot mol^{-1}\cdot min^{-1}}$ and $3.2\times10^{-4}\ \mathrm{min^{-1}\cdot l^2\cdot mol^{-2}}$, respectively. Thus, the ratio of k_c to k_b has been calculated as $0.46\ \mathrm{mol^{-1}\cdot l}$ indicating that the reaction of **1** with ethylenediamine is mildly accelerated. Assuming k_{-a} is much less than $(k_b+k_c[\mathrm{RNH_2}])$, Eq. 4 simplifies to $k'=k_a$ and the reaction is not base catalyzed. The reaction of **2** may correspond to this instance.

Kinetics of Copper(I) Catalyzed Reactions. The pseudo-first order plots for the reaction using copper(I) bromide as a catalyst were not linear (Fig. 1) presumably indicating that the reaction rate decreased with the formation of the ineffective copper(II) species. The rate equation has been interpreted as first order in concentration of bromoanthraquinones (AQBr) and copper(I) species. Thus,

$$-\frac{d[\mathrm{AQBr}]}{dt} = (k_0+k_1[\mathrm{CuBr}])[\mathrm{AQBr}], \qquad (6)$$

where k_0 denotes the pseudo-first order rate constant (k_I[EN] or k_II[EN]) of the catalyst-free reactions.

ESR measurements suggested that the copper(I) species was oxidized to the copper(II) species exponentially increased during the course of reaction. Then, the concentration of CuBr may be mathematically expressed by Eq. 7:

$$[\mathrm{CuBr}] = a\cdot\exp(-\gamma t) + b. \qquad (7)$$

The initial concentration of CuBr is given by

$$[\mathrm{CuBr}]_0 = a + b, \qquad (8)$$

and the concentration of CuBr approaches b after prolonged reaction.

Combining Eq. 6 with Eq. 7 and integrating gives Eq. 9.

$$-\ln(1-x) = \frac{k_1 a}{\gamma}(1-\mathrm{e}^{-\gamma t}) + (k_1 b+k_0)t \qquad (9)$$

This may be rewritten:

$$-\frac{\ln(1-x)}{t} = A\cdot\frac{(1-\mathrm{e}^{-\gamma t})}{t} + B, \qquad (10)$$

where x denotes the yield of the condensation product, and $A = k_1 a/\gamma$ and $B = k_1 b + k_0$. By assuming a value of γ, A and B were determined by means of linear regression analysis. The values of the parameters (A, B, and γ), which gave the maximum correlation coefficient, were taken to be the most suitable parameters. The agreement between calculated and observed data was very good, since the correlation coefficients were greater than 99% in all cases.

The rate constant k_1 can be obtained from Eq. 11,

$$k_1 = \frac{\gamma A + B - k_0}{[\mathrm{CuBr}]_0} \tag{11}$$

and the values of k_1 and γ are summarized in Tables 1 and 2. Tables 1 and 2 show that the rate constant k_1 is approximately independent of the initial concentration of CuBr. The plot of γA against the initial concentration of CuBr gives a straight line supporting the assumption that the condensation with ethylenediamine is first order with respect to copper(I) bromide. The values of the ratio $b/(a+b)$ are given by Eq. 12:

$$\frac{b}{a+b} = \frac{B - k_0}{\gamma A + B - k_0}. \tag{12}$$

Table 1. Rate constant k_1, γ, and the value of $b/(a+b)$ for the reaction of 1-bromoanthraquinone (**1**) with ethylenediamine (EN)

	mol·l^{-1}	k_1 (l·mol^{-1}·min^{-1})	γ	$\frac{b}{a+b}\times 100$ (%)
EN	0.256	17±0.5	0.16	0.9
	0.502	23±1	0.17	2.0
	0.669	23±0.5	0.17	8.6
	0.998	25±0.5	0.12	3.3
	1.410	31±1	0.15	6.2
CuBr	3.72×10^{-4}	15±1	0.14	0
	7.57	26±2	0.16	3.4
	10.7	23±1	0.17	2.0
	15.2	23±1	0.18	3.1
1	1.07×10^{-3}	26±0.5	0.07	12.8
	2.50	22±1.6	0.11	7.2
	5.02	23±1	0.17	2.0
	7.53	23±1	0.19	1.2
	10.1	20±1	0.20	0

Temp 70 °C, solvent 1,2-dimethoxyethane–methyl cellosolve 4: 1.

Table 2. Rate constant k_1, γ, and the value of $b/(a+b)$ for the reaction of 1-amino-4-bromoanthraquinone (**2**) with ethylenediamine (EN)

	mol·l^{-1}	k_1 (l·mol^{-1}·min^{-1})	γ	$\frac{b}{a+b}\times 100$ (%)
EN	0.260	23±2	0.29	2.1
	0.516	29±3	0.26	2.9
	0.747	33±2	0.25	4.1
	1.00	34±3	0.19	4.8
	1.42	40±2	0.18	8.0
CuBr	4.34×10^{-4}	47±4	0.27	3.1
	7.07	33±2	0.26	2.9
	9.51	29±3	0.26	2.9
	11.76	32±3	0.27	3.2
2	2.59×10^{-3}	29±1	0.15	2.7
	5.01	29±3	0.26	2.9
	7.54	23±3	0.35	1.2
	10.03	21±4	0.35	1.7

Temp 70 °C, solvent 1,2-dimethoxyethane–methyl cellosolve 4: 1.

As shown in Tables 1 and 2, the value of $b/(a+b)$ was less than about 4% in most cases indicating that the copper(I) species is almost perfectly oxidized to the copper(II) species after prolonged reaction.[7] Under these condensation conditions debrominated products were also produced suggesting that the copper(II) species was formed by an electron transfer from copper(I) to bromoanthraquinone ($\mathrm{AQBr} + \mathrm{Cu(I)} \longrightarrow \mathrm{AQBr}^{\bullet} + \mathrm{Cu(II)}$) in a similar manner to the condensation with 2-aminoethanol and that part of the resulting bromoanthraquinone anion radical may be debrominated.[4]

The catalytic activity of copper(I) species in the reaction with ethylenediamine was insensitive to the resulting copper(II) species. This is presumably because ethylenediamine strongly coordinates to the copper(II) species and thereby prevents cooperation between the copper(I) and copper(II) species. It has been reported that copper(II) forms stable chelate complex with ethylenediamine ($[\mathrm{Cu(EN)}]^{2+}$ and $[\mathrm{Cu(EN)_2}]^{2+}$).[8]

The catalytic activity of the copper(I) species in the reaction with ethylenediamine was 20 times greater than that with 2-aminoethanol. After a statistical correction of 2 was applied, ethylenediamine was more reactive than 2-aminoethanol by a factor of 10. This has been attributed to the fact that electrons are more delocalized in the copper(I) species with a bidentate amine such as ethylenediamine.

Reaction Mechanism. As indicated in Tables 1 and 2, the rate constant k_1 increased with increasing concentration of amine, the plot of $1/k_1$ against $1/[\mathrm{EN}]$ giving a linear relationship (Fig. 2). On the other hand, the rate constant k_1 decreased with increasing concentration of bromoanthraquinone ([AQBr]), the plot of $1/k_1$ against [AQBr] giving a straight line (Fig. 3).

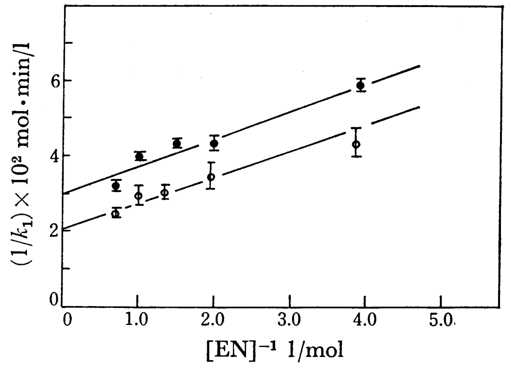


Fig. 2. Plots of $1/k_1$ against $1/[\mathrm{EN}]$. Temp 70 °C, solvent 1,2-dimethoxyethane–methyl cellosolve 4: 1.
●: 1-BrAQ–EN–CuBr, ○: 1-NH$_2$-4-BrAQ–EN–CuBr.

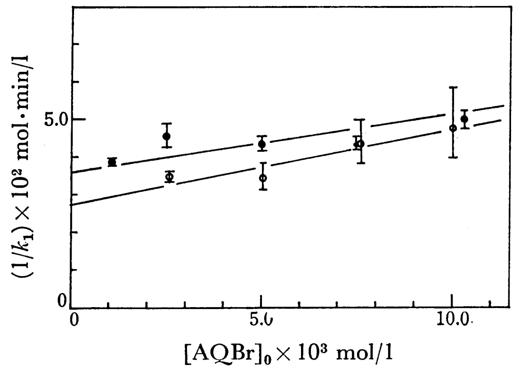


Fig. 3. Plots of $1/k_1$ against [AQBr]. Temp 70 °C, solvent 1,2-dimethoxyethane–methyl cellosolve 4: 1. ●: 1-BrAQ–EN–CuBr ○: 1-NH_2-4-BrAQ–EN–CuBr.

All results can be interpreted by assuming the following reaction scheme (Eq. 13):

$$\begin{aligned} &Cu^{I} + EN \overset{K_1}{\rightleftarrows} Cu^{I}(EN) \\ &Cu^{I} + AQBr \overset{K_2}{\rightleftarrows} Cu^{I}(AQBr) \xrightarrow[k_r]{EN} \text{product.} \end{aligned} \tag{13}$$

On the basis of this (Eq. 13), the rate constant k_1 is expressed by

$$k_1 = \frac{k_r K_2[EN]}{1+K_1[EN]+K_2[AQBr]}. \tag{14}$$

The concentration of AQBr under smal conversion is approximately equal to the initial concentration ($[AQBr]_0$). Thus equation 14 may be rewritten:

$$k_1^{-1} = \frac{k_1}{k_r K_2} + \frac{1+K_2[AQBr]_0}{k_r K_2}\cdot\frac{1}{[EN]}, \tag{15}$$

$$k_1^{-1} = \frac{1+K_1[EN]}{k_r K_2[EN]} + \frac{K_2}{k_r K_2[EN]}\cdot[AQBr]_0. \tag{16}$$

The values k_r, K_1, and K_2 can be evaluated from the slope and the intercept of Figs. 2 and 3, and the concentrations of AQBr and EN, the values of which are shown in Table 3. Since the equilibrium between Cu^{I} and EN does not include haloanthraquinone, there should not be any difference in the magnitude of K_1 between **1** and **2**. Table 3 shows that K_1 in the reaction of **1** is approximately equal to that in the reaction of **2**, which supports the above mechanism.

The parameter γ corresponds to the decreasing rate of copper(I) species. As shown in Tables 1 and 2, the magnitude changes with the initial concentrations of haloanthraquinone and copper(I) bromide, but it is little affected by the concentration of amine. The kinetics of the formation of the copper(II) species, however, is not yet clearly understood.

TABLE 3. RATE PARAMETERS

Rate parameter	1-BrAQ (**1**)	1-NH_2-4-BrAQ (**2**)
k_r ($mol^{-1}\cdot l\cdot min^{-1}$)	1.24	0.98
K_1 ($l\cdot mol^{-1}$)	8.9	10.0
K_2 ($l\cdot mol^{-1}$)	243	500

Temp 70 °C, solvent 1,2-dimethoxyethane–methyl cellosolve 4: 1, $[AQBr]_0=5\times 10^{-3}$ $mol\cdot l^{-1}$, $[EN]_0=5\times 10^{-1}$ $mol\cdot l^{-1}$.

As previously reported, in the presence of copper(I) catalyst, **1** is more reactive than **2** and this may be reasonably explained as follows: The rate constant k_r of **2** is smaller than that of **1**, while the equilibrium constant between Cu(I) and **2** has a greater value than that between Cu(I) and **1**. Thus, **2** has an initial rate similar to that of **1**. The reaction rate of **2**, however, diminishes more rapidly than that of **1** with time, an observation caused possibly by the concentration of copper(I) species decreasing more rapidly in the reaction of **2** than in the reaction of **1**, since the magnitude of the parameter γ of **2** is greater than that of **1**.

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