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Copper(I)-Induced Halogen–Hydrogen Exchange of 2-Halogenoanilines

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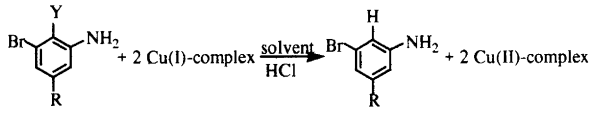
The copper(I)-induced halogen–hydrogen exchange in the 2-position of 2,3-dibromoaniline, 2.3-dibromo-5-methylaniline, 2,3-dibromo-5-chloroaniline and 3-bromo-2-iodoaniline has been studied in acetic acid, ethanol and chlorobenzene media with a hydrochloric acid content of 0.56 mol dm^{-3}. The CuX_3^{2-} complexes used in the reduction reaction are $(CH_3Ph_3P^+)_2\,CuBr_3^{2-}$, $(CH_3Ph_3P^+)_2\,CuI_3^{2-}$, $(NH_4^+)_2\,CuBr_3^{2-}$ and $(NH_4^+)_2\,CuCl_3^{2-}$. $(C_4H_9)_4N^+\,CuCl_2^-$ and $NH_4^+\,CuBr_2^-$ have also been tested in the same media. The reduction rate increases with the size of the Cu(I)-complex.

The copper(I) chloride-induced dehalogenation in the 2-position of 5-substituted 2,3-dibromoanilines in aqueous acetic acid–hydrochloric acid medium, with [Cl^-] ranging from 2.0 to 5.25 mol dm^{-3}, has previously been studied kinetically.[1] At a chloride ion concentration of 2.0 mol dm^{-3} the dehalogenation reaction was hardly detected, but at 5.25 mol dm^{-3}, where $CuCl_3^{2-}$ was presumed to be the dominating Cu(I) species, the reduction rate could be followed to 80% consumption of the substrate without formation of by-products. It was proved that two Cu(I)-complexes had disappeared for every molecule of substrate reduced and two Cu(II)-complexes were generated. The kinetics of the reduction reaction was seen to follow second-order kinetics, first order in both aniline and copper(I). A substituent in the 4-position to the reaction center increased the rate of reduction.[1]

In the present investigation we have used crystalline inorganic and organic salts as sources of the CuX_3^{2-} complexes to verify the suggestion that this copper(I) complex is the active species in the halogen–hydrogen exchange. We have examined the reduction reaction of 5-substituted 2,3-dihalogenoanilines in the following solvents: acetic acid, ethanol, chlorobenzene and dimethyl sulfoxide. Hydrochloric acid (conc. aqueous) was added. The hydrochloric acid concentration of the medium was restricted to 0.56–1.1 mol dm^{-3} and the copper(I) ion concentration to 0.097–0.144 mol dm^{-3} to avoid higher copper(I) complexes being formed (Scheme 1).



1 Y = Br, R = H
2 Y = Br, R = CH_3
3 Y = I, R = H
4 Y= Br, R = Cl

Scheme 1.

Results

The copper(I)-induced reduction of 5-substituted 2,3-dihalogenoanilines was performed at 80–90°C in the above-mentioned solvents. The Cu(I) complexes, selected as reducing agents, were bis(methyltriphenylphosphonium) tribromocuprate(I) (**5**), bis(methyltriphenylphosphonium) triiodocuprate(I) (**6**), diammonium trichlorocuprate(I) (**7**), diammonium tribromocuprate(I) (**8**), ammonium dibromocuprate(I) (**9**) and tetrabutylammonium dichlorocuprate(I) (**10**).

The structure of these copper(I) complexes in the crystalline state is documented,[2–4] but the structure of the complexes in an organic solvent is uncertain. With the intention of elucidating this, a series of UV investigations in abs. ethanol and in ethanol–hydrochloric acid were carried out. The low solubility of the salts at 25°C, however, prevented us from working with the same concentrations as in the kinetic studies.

The reduction reactions were followed by means of GLC, ^{1}H NMR spectroscopy and mass spectrometry. The reduction only occurred when the Cu(I) complex and the hydrochloric acid (or hydrobromic acid) were present. (See Table 1). When HCl was replaced by $HClO_4$, while other conditions remained unchanged, the reduction failed. Apparently, chloride ion (or bromide ion) has to be present for the reaction to take place.

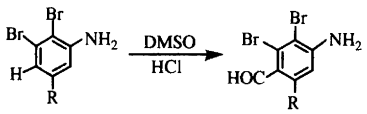
In the DMSO–HCl solvent mixture, [HCl] = 0.56 mol dm^{-3}, an unexpected result was obtained. Compounds **1** and **2**, which were treated in this solvent mixture, gave, with salt **7**, only a small yield of the

Table 1. Rate constants for Cu(I)-induced bromine–hydrogen exchange in the 2-position of substituted 2,3-dibromoanilines (0.045–0.048 mol dm^{-3}). [Cu(I)-complex] is 0.097–0.144 mol dm^{-3}. [HCl] of the solvents is 0.56 mol dm^{-3}.

Substrate	Cu(1)-complex	Solvent	T/°C	$k_2/10^{-4}$ $M^{-1}s^{-1}$ [a]
2,3-Dibromoaniline **1**	$(NH_4^+)_2\,CuCl_3^{2-}$ **7**	AcOH	90.0	0.45(4)
1	$(NH_4^+)_2\,CuBr_3^{2-}$ **8**	AcOH	90.0	2.39(7)
1	**8**	AcOH[b]	90.0	9.2[c]
1	**8**	EtOH	80.0	0.49(3)
2,3-Dibromo-5-chloroaniline **4**	**7**	AcOH	90.0	1.83(24)
4	**7**	EtOH	80.0	0.07(1)
4	**8**	EtOH	80.0	1.31(16)
2,3-Dibromo-5-methylaniline **2**	**7**	AcOH	90.0	4.10(40)
2	**7**	AcOH[d]	90.0	4.17(32)
2	**7**	EtOH	80.0	0.33(1)
2	$(C_4H_9)_4N^+CuCl_2^-$ **10**	AcOH	90.0	6.31(37)
2	CuCl	AcOH–H_2O	90.0	5.77(28)[e]
2	**8**	AcOH	90.0	18.2(13)
2	**8**	EtOH	80.0	3.83(25)
2	$NH_4^+CuBr_2^-$ **9**	EtOH	80.0	3.24(44)
2	$(Ph_3MeP^+)_2CuBr_3^{2-}$ **5**	AcOH	90.0	38.0(53)
2	**5**	EtOH	80.0	6.59(45)
2	**5**	ArCl	90.0	29.4(51)
2	$(Ph_3MeP^+)_2CuI_3^{2-}$ **6**	AcOH	80.0	77.5(101)
2	**6**	EtOH	80.0	24.6(26)
2	**6**	ArCl	90.0	42.1(139)

[a] 2-4 different runs in each calculation. Uncertainties are two standard deviations from least-squares method calculations. The observed k_2 is a summation of contributions from all catalytic Cu(I)-containing species present. [b] HCl in the medium is replaced by HBr (0.56 mol dm^{-3}). [c] Initial value. [d] [HCl] = 1.1 mol dm^{-3}. [e] Value from Ref. 1, [HCl] = 5.25 mol dm^{-3}.

corresponding 2-H compounds, the main product being 4-aminobenzaldehyde with ring-halogenated by-products. A closer examination of the aldehyde synthesis from the current substrates in DMSO–HCl has been undertaken.[5] The chloromethyl methyl sulfoxide, formed in the reaction of DMSO with HCl, is probably the reactive species in the aldehyde formation. The copper salt, however, is not necessary for this reaction (Scheme 2).



1 R = H
2 R = CH_3

Scheme 2.

The reduction in the 2-position of 2,3-dibromoaniline (**1**), 2,3-dibromo-5-methylaniline (**2**) and 2,3-dibromo-5-chloroaniline (**4**), induced by the Cu(I) complexes **5**–**10**, in the solvents acetic acid, ethanol and chlorobenzene ([HCl] = 0.56 mol dm^{-3}) was followed kinetically up to 50–87% consumption of the substrate, depending on when the formation of by-products started (Table 1). The reactions were interrupted when the formation of by-products exceeded 2%.

The reduction rate was seen to depend on the size of both the anion and the cation in the salts of the Cu(I) complexes. When in the reduction reaction of **1** with $(NH_4^+)_2\,CuBr_3^{2-}$ the anion $CuBr_3^{2-}$ had Br^- instead of Cl^- as the supporting ligand, the reduction rate increased by a factor of four (acetic acid–HBr). Compared with the reduction of **1** with $(NH_4^+)_2\,CuCl_3^{2-}$ as the reducing agent in acetic acid–HCl solvent the above-mentioned reduction rate was enhanced by a factor of 20. The dependence of the solvent was $CH_3COOH > C_2H_5OH \approx C_6H_5Cl$ with only small differences (Table 1). The conclusion from these solvent effects is that the polarity, as well as the polarisability of the solvent, control the reduction rate.[6] A substituent in the 5-position enhanced the reduction rate: $CH_3 > Cl > H$, which agreed with the results from previous work.[1]

The copper(I)-induced reduction in the 2-position of 3-bromo-2-iodoaniline (**3**) is not so clear. The reduction by means of salts **7** and **8** was examined in acetic acid and ethanol with a chloride ion concentration of 0.56 mol dm^{-3} and revealed non-linear kinetics. After a reaction time of 20–30 min with salt **8** in acetic acid at 90°C a maximum in the reduction was noticed; about 80% of the substrate was reduced to 3-bromoaniline. If a few drops of a starch solution were added, the blue starch–iodide complex was formed when about 50% of the substrate was reduced and could be proved until the maximum point. Subsequent iodination in the 2-position of the 3-bromoaniline occurred and after 60–70 min about 70% of the starting substance **3** was obtained; no starch–iodide complex was detectable. We have not been

Table 2. Cu(I)-induced iodine–hydrogen interchange of 3-bromo-2-iodoaniline (**3**) (0.048 mol dm^{-3}) in the 2-position. [Cu(I)-complex] is 0.144 mol dm^{-3}. [HCl] of the solvent is 0.56 mol dm^{-3}.

Cu(I)-complex	Solvent	T/°C	t/min	ArH_{max} (%)	t/min	ArH (%)
$(NH_4^+)_2\,CuBr_3^{2-}$ **8**	AcOH	90.0	20–30	80	60–70	30
8	EtOH	80.0	50–60	50	90–100	30
$(NH_4^+)_2\,CuCl_3^{2-}$ **7**	AcOH	90.0	20–30	55	60–70	30

able to obtain more than one cycle. The maximum point of the reduction reaction and t_{max} could not be exactly repeated; they seem to depend on the starting pulse of the reaction. With salt **7** in acetic acid the reduction was somewhat slower. In ethanol (80°C) with salt **8** as the reducing agent, the maximum was attained after 50 to 60 min with about 50% of the substrate being reduced (Table 2).

Discussion

The results of our UV investigation of the copper(I) salts **5**–**11** in ethanol and ethanol–HCl solvents agree in principle with previous reports (see the Experimental). Sugasaka and Fujii[7] have investigated the copper(I) chloride complexes in aqueous acidic solution (Cl^-, ClO_4^-) by spectrophotometry. With a chloride ion concentration of 0.05–5.0 mol dm^{-3} they observed only $CuCl_2^-$ and $CuCl_3^{2-}$ anions, at 273 nm the $CuCl_3^{2-}$ complex is stated to be the only absorbing species, but at 233 nm both the $CuCl_2^-$ and $CuCl_3^{2-}$ complexes are assumed to absorb. They calculated the equilibrium constant K_3 for eqn. (1).

$$CuCl_2^- + Cl^- \rightleftarrows CuCl_3^{2-} \qquad K_3 = 1.95\ M^{-1} \qquad (1)$$

By the solubility method Hikita *et al.*[8] have determined K_3 to be 0.97 M^{-1}. Ahrland and Tagesson[9] found, by potentiometric measurement, K_3 to be 0.76 M^{-1} (aqueous medium, ClO_4^-, 25°C). Stevenson *et al.*[10] reported an absorption maximum for $CuCl_2^-$ at 233 nm and a shoulder at 274 nm and for $CuCl_3^{2-}\lambda_{max}$ at 276 nm and a shoulder at 230 nm (1 M H^+, ClO_4^-, aqueous solution).

Our present work deals with crystalline CuX_3^{2-} salts dissolved in organic solvents with added conc. hydrochloric acid. However, the reported values for K_3 may serve as a very rough estimate of the $CuCl_3^{2-}$ concentration at $t = 0$. Without the addition of HCl $[CuCl_3^{2-}]_0$ may be small. When assuming the CuX_3^{2-} complex anions to be the species responsible for the reduction of the halogenoanilines, one understands why $(NH_4^+)_2\,CuCl_3^{2-}$ in acetic acid without added hydrochloric acid leads to no reduction. The anions $CuBr_3^{2-}$, as well as CuI_3^{2-}, have larger K_3 values, 14.8 and 56.3 M^{-1},[9] respectively (aqueous medium, ClO_4^-). Higher $[CuBr_3^{2-}]_0$ and $[CuI_3^{2-}]_0$ are thus to be expected. This is also reflected in the reduction in the present work (Table 1).

Andersson *et al.*[11] have performed far-IR investigations of $[(CH_3)_4P^+]_2\,CuBr_3^{2-}$ in nitromethane. They reported only a band at 324 cm^{-1}, assigned to the $CuBr_2^-$ monomer, and concluded that $CuBr_2^-$ appears to be the dominant and probably the sole bromocuprate(I) species in nitromethane.

In the solution of CuI_3^{2-} it cannot be excluded that higher mixed complexes are present in spite of the low chloride ion concentration.[9]

In our previous investigation[1] with copper(I) chloride in hydrochloric acid–water–acetic acid medium, [HCl] = 5.25 mol dm^{-3}, a higher $[CuCl_3^{2-}]_0$ was present. It was possible to follow the reduction reaction to 80% completeness without the appearance of by-products. The reduction rates in the aqueous medium were comparable to the rates observed in acetic acid–HCl in the present investigation (Table 1).

From our previous ^1H NMR investigations of tetrabutylammonium dihalogenocuprates(I) in chlorobenzene, chloroform and acetone we have concluded that these Cu(I) salts are present as loose ion pairs in the solvents of interest.[12] A larger cation will result in a greater interionic distance and thus a looser ion pair, the cation–anion interaction will be reduced and a more reactive anion will be created. Our results in the present work also agree with this (*vide supra*).

The fact that the reduction rate varies by only a factor of two to three in acetic acid, ethanol, chlorobenzene ([HCl] = 0.56 mol dm^{-3}) and acetic acid–water–hydrochloric acid [[HCl] = 5.25 mol dm^{-3})[1] and that a substituent in the 4-position to the reaction center, irrespective of a negative or a positive σ_p-value, enhanced the reaction rate, leads us to suggest a radical-forming reaction.[13] The observed reduction rates, increasing with the anions $CuCl_3 < CuBr_3 < CuI_3$, in the order of decreasing bond strength, can also be justified by an electron-transfer mechanism. Two Cu(I) complexes are oxidized to two Cu(II) complexes for every substrate molecule reduced.[1] We propose two one-electron steps and an intervening bond-cleavage step, eqns. (2)–(4).

$$ArY + Cu^{I}X_3^{2-} \rightarrow ArY^{\cdot -} + Cu^{II}\text{-complex} \qquad (2)$$

$$ArY^{\cdot -} \rightarrow Ar^{\cdot} + Y^- \qquad (3)$$

$$Ar^{\cdot} + Cu^{I}X_3^{2-} + H^+ \rightarrow ArH + Cu^{II}\text{-complex} \qquad (4)$$

The first step is believed to be slow and rate determining. In the transition state internal and solvent reorganizations (λ_i and λ_o) contribute to the energy of the activated complex and the electron-transfer rate.[14] Increasing solvent polarity increases λ_o, but in organic solvents λ_o is only a minor part of λ. The λ-values fall in order of decreasing Cu–X bond strength. A substituent in the 4-position to the reaction center causes the charge in the transition state to be delocalized over a more sizable volume and λ will be lowered.[14] However, other

likely alternatives may explain the reaction route of the reduction.

The different behaviour of the 2-iodoanilines compared with the 2-bromoanilines under the prevailing conditions is probably a consequence of the ability of the iodide ion, formed in step (3), to be oxidized in acidic solution. The Cu(II) complex, formed in steps (2) and (4), can serve as the oxidizing agent. The I^- ion concentration is low at the beginning of the reduction, I_2 is rapidly produced and reaches a maximum.[15] The I_3^- ion produces the blue color

$$I_2 + I^- \rightleftarrows I_3^- \qquad K_{eq} = 723\ M^{-1}\ ^{16} \tag{5}$$

with starch.[17] After I_2 has reached its maximum it is consumed and 3-bromo-2-iodoaniline, the starting substance, is produced. The reaction mixture then gives no more blue iodide–starch complex.

$$ArH + I_2 \rightarrow ArI + H^+I^- \tag{6}$$

No second cycle could be observed. It is most likely that the active Cu(I) complex changed its original structure in the reversible process [eqn. (7)]. The latter

$$\text{Cu(I) complex} \rightleftarrows \text{Cu(II) complex} \tag{7}$$

form may not have the potential of reducing the 3-bromo-2-iodoaniline.

Experimental

Melting points were determined with a Koflerhot-stage melting point microscope and are uncorrected. The ^{1}H NMR spectra were obtained on a Varian XL-400 NMR spectrometer with $(CH_3)_4Si$ as internal standard. Mass spectra were recorded on a Finnigan 1020 B instrument (E_i 70 eV), IR spectra on a Perkin-Elmer 1600 FT infrared spectrometer and UV spectra with a Varian Cary 4 UV–VIS spectrophotometer equipped with a Hewlett Packard 7475 A plotter. The GLC investigations were carried out on a Perkin-Elmer 3920 B instrument with a Hot Wire Detector with He as the carrier gas. Calibration curves were obtained from known mixtures of pure anilines. All reactions were performed in an argon (dried) atmosphere and in the dark.

All solvents used in the reactions were dried and distilled. The synthesis of compounds **1**, **2** and **4** is described in Ref. 1. The hydrochloric acid strength of the medium was determined as $[Cl^-]$ through Mohrs titration, which gave a $[Cl^-] = 0.56$ mol dm^{-3}. The experimental procedures are described in Ref. 1.

3-Bromo-2-iodoaminobenzene (**3**) was prepared from 3-bromo-2-iodonitrobenzene (1.4 g, 0.004 mol) by reduction with iron (0.8 g, 0.012 mol) in 50% ethanol (10 ml), acidified with conc. HCl (0.5 ml). The reaction mixture was refluxed for about 2 h, was then made alkaline and the product extracted with diethyl ether. Yield 0.9 g (76%). After sublimation the m.p. was 46.2–47.0°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.64 (H-6, q, *J* 7.1 and 2.15 Hz), 6.97 (H-5, q, *J* 7.1 Hz), 7.01 (H-4, q, *J* 7.1 and 2.15 Hz), 4.33 (2 H, NH_2, s). MS: *m/z* (% rel. intensity) 297 (100), 299 (96), 172 (28), 170 (25).

Bis(methyltriphenylphosphonium) tribromocuprate(I), $(MePh_3P^+)_2\ CuBr_3^{2-}$ (**5**), *bis(methyltriphenylphosphonium) triiodocuprate(I), $(MePh_3P^+)_2\ CuI_3^{2-}$* (**6**) *and methyltriphenylphosphonium dibromocuprate(I), $MePh_3P^+\ CuBr_2^-$* (**11**) were prepared according to Bowmaker *et al.*[2]

5. M.p. 143.0–143.8°C. IR (KBr): a doublet at 880, 887 cm^{-1}. UV (abs. ethanol or ethanol–hydrochloric acid): λ_{max} at 225, at 262, 267, 273 nm (shs).

6. M.p. 161.3–162.1°C. IR (KBr): a doublet at 891, 905 cm^{-1}. UV (abs. ethanol or ethanol–hydrochloric acid): λ_{max} at 220, at 262, 267, 274 nm (shs).

11. M.p. 110–112°C. IR (KBr): a doublet at 910, 915 cm^{-1}. UV (abs. ethanol or ethanol–hydrochloric acid) λ_{max} at 225, at 261, 267, 274 nm (shs).

Diammonium trichlorocuprate(I), $(NH_4^+)_2\ CuCl_3^{2-}$ (**7**), *diammonium tribromocuprate(I), $(NH_4^+)_2\ CuBr_3^{2-}$* (**8**) *and ammonium dibromocuprate(I), $NH_4^+\ CuBr_2^-$* (**9**) were synthesized according to Refs. 3 and 4. Tetrabutylammonium dichlorocuprate(I), $(C_4H_9)_4N^+CuCl_2^-$ (**10**) was available.[12]

7. IR (KBr): 3154, 1402 cm^{-1}. UV (abs. ethanol or ethanol–HCl): λ_{max} at 229, 284 nm (sh).

8. IR (KBr): 3173, 1396 cm^{-1}. UV (abs. ethanol): λ_{max} at 235 nm, (ethanol–HCl): λ_{max} 230, at 287, 365 nm (shs).

9. IR (KBr): 3144, 1396 cm^{-1}. UV (abs. ethanol): λ_{max} at 235 nm, (ethanol–HCl): λ_{max} 230, at 283, 365 nm (shs).

10. UV (abs. ethanol): λ_{max} at 229 nm, (ethanol–HCl): λ_{max} at 229, 285 nm (sh).

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