Copper(I) as a Homogeneous Catalyst for the Ullmann Reaction in Aqueous Solutions − The Transformation of 2-Bromobenzoate into Salicylate

Magal Saphier,*[a,b] Alexandra Masarwa,[a] Haim Cohen,[a,b] and Dan Meyerstein[a,c]

Keywords: Copper(I) / Aromatic compounds / Catalysis / Ullmann reaction

The Cu^I-catalyzed transformation of 2-bromobenzoic acid (2-Br-BA) into salicylic acid (main product), benzoic acid, and diphenoic acid was studied. The reaction was monitored by UV/Vis spectroscopy, HPLC, and ESR. Up to 25 turnovers were achieved for low Cu^I concentrations. An intermediate was observed that was assigned to a complex between copper and a follow-up product of the aromatic acid, probably a complex with a copper–carbon σ-bond. The process is probably initiated by the formation of a d-π* complex of Cu^I with the aromatic ring of 2-Br-BA followed by the reaction with a second Cu^I ion. The effect of the addition of CH_3CN or NH_3 on the catalytic process is reported. Both were found to accelerate the process when present at relatively low concentrations and slow it down at higher concentrations. A side product, 2-aminobenzoate was observed in the presence of NH_3.

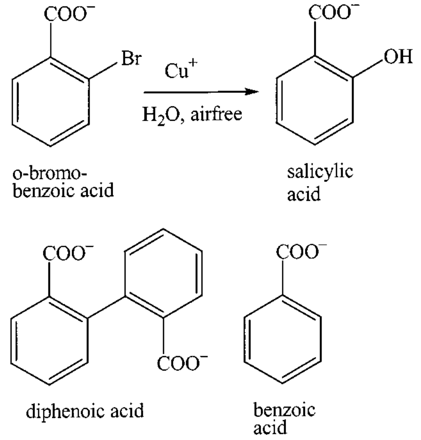
Introduction

Copper(I) complexes are key intermediates in a variety of catalytic processes in aqueous solutions, e.g. the catalytic substitution of halogens at the aromatic ring by nucleophiles in the presence of copper(I) (Ullmann reaction).[1] The expected steady-state concentration of Cu^+_{aq} is extremely low due to the disproportionation of Cu^+_{aq} [Equation (1)[2]] and the low solubility of cuprous oxide/hydroxide[2] and halides.[2] Moreover, atmospheric dioxygen, dissolved in water, reacts rapidly with copper(I) oxidizing it to copper(II). The addition of stabilizing ligands can increase the concentration of copper(I) in aqueous solutions and thus improve the efficiency of the catalytic process. However, these ligands are also expected to affect the reactivity of Cu^I, i.e. stabilizing ligands are in principle expected to decrease the Cu^I reactivity and therefore to slow down the catalytic process. A well-known method for the preparation of Cu^I solutions is the addition of CH_3CN.[2] Recently, it was reported that a series of aromatic compounds, such as 2-chlorobenzoic acid, form relatively stable d-π* complexes with Cu^I and thus increase Cu^I concentration in solution.[3]

$$Cu^{2+} + Cu^0 \rightleftarrows 2\,Cu^+_{aq} \quad K_{aq} = 1.00 \cdot 10^{-6}\ \mathrm{M}^{-1} \tag{1}$$

$$Cu^+_{aq} + L \rightleftarrows CuL^+_{aq} \tag{2}$$

It was therefore of interest to study the implications, in terms of the mechanism of the catalytic process, of the addition of ligands in general and of Cu^I d-π* complex formation with aromatic compounds. In this study, the copper(I)-catalyzed substitution of halogen atoms at an aromatic ring was studied. As a model reaction, the transformation of 2-bromobenzoic acid into salicylic acid, benzoic acid, and diphenoic acid was chosen (Scheme 1).



Scheme 1

Results

On addition of Cu^I to deoxygenated aqueous solutions of 2-bromobenzoic acid (2-Br-BA) a relatively slow reaction takes place yielding salicylic, diphenoic, and benzoic acid. The kinetics of this process can be monitored by UV/Vis spectrophotometry. A peak at 296 nm grows in intensity,

---

[a] Chemistry Department Ben-Gurion University of the Negev, Beer-Sheva, Israel
E-mail: massarwa@bgumail.bgu.ac.il
[b] Nuclear Research Centre Negev
Beer-Sheva, Israel
[c] The College of Judea and Samaria,
Ariel, Israel

1434−1948/02/0505−1226 $ 20.00+.50/0

which is attributed to salicylate. The spectra of possible products of the reaction are shown in Figure 1. Moreover, organic products and the starting material can be identified and quantified by HPLC.

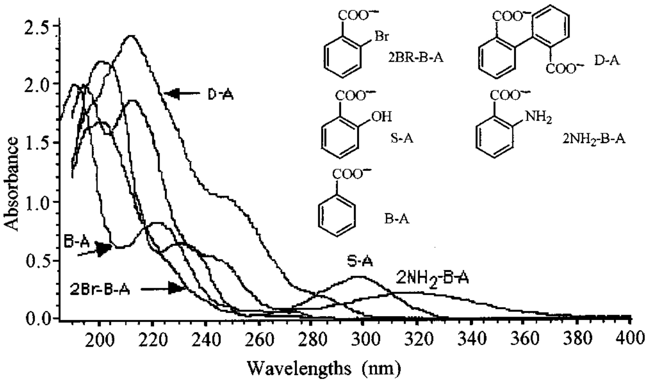


Figure 1. UV/Vis spectra of possible organic products and starting material (all 0.1 mM in aqueous solution)

The following sources of Cu^I were used in the course of this study:

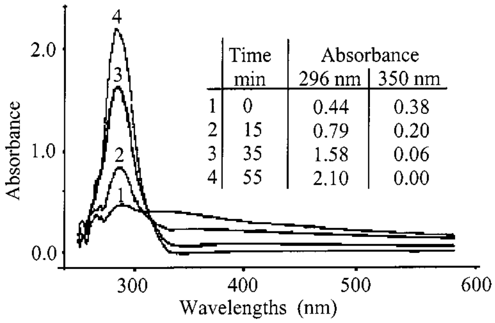
1. Commercially available $Cu(CH_3CN)_4PF_6$ salt was added to deaerated aqueous solutions of *o*-bromobenzoic acid after addition of CH_3CN. Under these conditions, Cu(OH) precipitated (yellowish) only at $pH > 9$, whereas it precipitated already at $pH = 7$ without the addition of stabilizing ligands.

2. $[Cu(CH_3CN)_4]^+$ was prepared by the comproportionation of Cu^{II}_{aq} (source $CuSO_4$) and Cu^0 metal in deaerated aqueous solutions containing CH_3CN. Complete comproportionation was achieved when the concentration of acetonitrile was above 4%, in accordance with literature data.[4] This method can also be performed with different stabilizing ligands, e.g. higher concentrations of ammonia at basic pH.[2] The resulting Cu^I solution was subsequently injected into deaeraeted aqueous solutions of 2-bromobenzoic acid.

3. During the course of this study it emerged that Cu^I could also be prepared in situ by comproportionation of $CuSO_4$ and Cu metal in deaerated aqueous solutions containing 2-bromobenzoic acid. The bromobenzoic acid is expected to lead to comproportionation according to the measured stability constants.[3] Note that these stability constants increase with the increase in pH.[3] The comproportionation in this system was complete, as verified by the fact that the detected amounts of Cu^I were more than twofold the initial $CuSO_4$ concentration (as the catalytic cycle already starts with the addition of the 2-bromobenzoic acid).

Kinetics of Formation of Salicylic Acid Monitored by UV/Vis Spectrophotometry

Figure 2 shows typical spectral changes occurring during the initial phase of the reaction of 2-Br-BA and Cu^I. The absorbance at 296 nm increased, due to the formation of salicylic acid (SA), while the absorbance in the 310−430 nm region decreased during the course of about 1 h under the specific conditions used. It should be noted that time "zero" in these experiments is ca. 10 min after the solution was prepared. The spectral changes in the 310−430 nm region are attributed to the decomposition of an initially formed intermediate. The slow reaction can best be monitored when Cu^I is prepared in situ by comproportionation of $CuSO_4$ (0.001−0.01 M) and Cu^0 in 2-Br-BA solution. Figure 3 shows typical kinetic traces at 296 and 350 nm implying several overlying reactions.



	Time min	Absorbance 296 nm	350 nm
1	0	0.44	0.38
2	15	0.79	0.20
3	35	1.58	0.06
4	55	2.10	0.00

Figure 2. UV/Vis spectral changes during the reaction of 2-Br-BA with Cu^+ [2-Br-BA (0.05 M), $CuSO_4$ (0.01 M), Cu^0, no air, $pH_{init} = 7.0$] (* 0-time is 10 min after mixing of the reactants, due to degassing time)

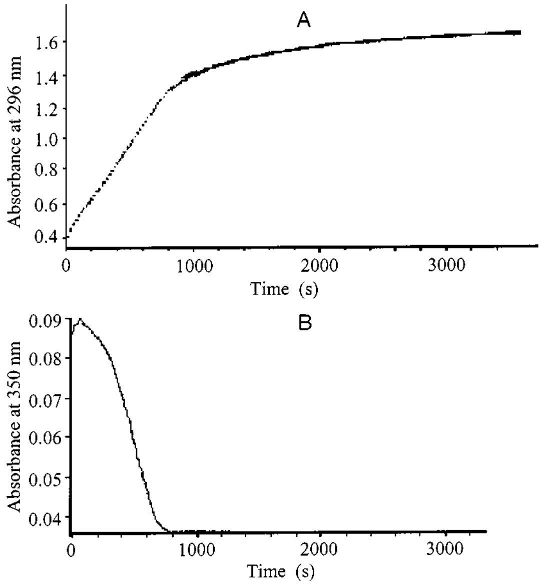


Figure 3. Kinetic traces monitored A) at 296 (SA) and B) at 350 nm (intermediate) during the reaction of 2-Br-BA with Cu^+ [2-Br-BA (12.5 mM), $CuSO_4$ (0.1 mM), Cu^0, 4% MeCN, no air, $pH_{init} = 6.7$)] (* 0-time is 10 min after mixing of the reactants, due to degassing time)

During the disappearance of the intermediate, the formation of salicylic acid is fastest, but it continues after that time. The amount of salicylic acid formed within 2 h [calculated according to its absorption at 296 nm ($\varepsilon = 3400$ $M^{-1}cm^{-1}$), if necessary after dilution] was found to be proportional to the initial concentration of 2-Br-BA (Figure 4) under conditions of excess 2-Br-BA and a given Cu^I concentration. This Cu^I concentration was supplied by $Cu(CH_3CN)_4PF_6$ (without any addition of CH_3CN in this case). The amount of salicylic acid formed was higher than the initial Cu^I concentration, implying a catalytic role of Cu^I. Moreover, varying the Cu^I salt concentration (employing ammonia as a stabilizing ligand) shows that the final amount of salicylic acid formed is independent of the initial Cu^I concentration (Figure 5), pointing again to its catalytic role. Up to 25 turnovers were achieved for the lowest Cu^I concentration and ca. 35% of the organic acid was converted under these specific conditions. The initial changes in salicylic acid (SA) concentration (d[SA]/dt calculated from the changes during the first 40 min of the reaction) are proportional to the square of the initial Cu^I concentration (Figure 6).

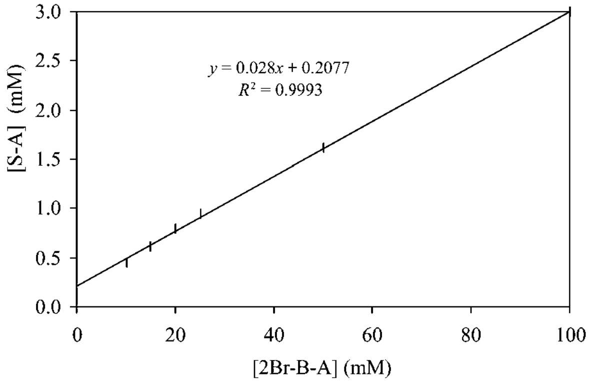


Figure 4. Dependence of SA production (after 120 min) on initial 2-Br-BA concentration {$Cu[MeCN]_4PF_6$ (0.33 mM), pH_{init} = 7.0}

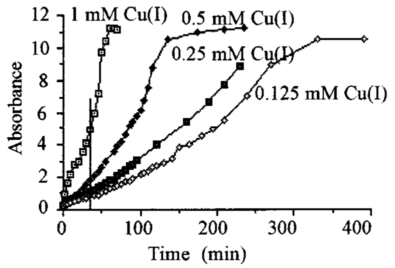


Figure 5. Kinetic traces monitored at 296 nm (SA) during the reaction of 2-Br-BA with Cu^+ for different initial Cu^+ concentrations {2-Br-BA (10 mM), $Cu[MeCN]_4PF_6$, NH_3 (0.0175 M), pH_{init} = 9.0} (* 0-time is 10 min after mixing of the reactants, due to degassing time)

Kinetics of the Formation of the Organic Products Monitored by HPLC

As the reaction is relatively slow, it is possible to monitor the formation of the organic products and decomposition of 2-Br-BA by HPLC. Figure 7 shows a typical kinetic run, with salicylic acid indeed being the main product of the process. Diphenoic acid formed with a similar kinetic profile, rate decreasing with the progress of the process, but with a significantly smaller yield. The formation of benzoic acid on the other hand was a slow but steady process, the final yield being similar to that of diphenoic acid, i.e. the relative yield of benzoic acid to that of salicylic, or diphenoic, acid increased with the progress of the reaction.

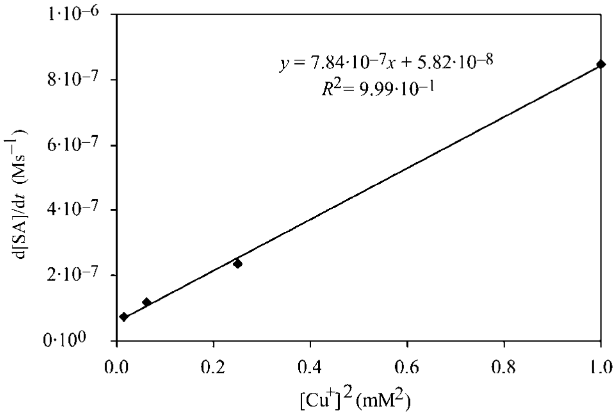


Figure 6. Dependence of SA production on the square of the initial Cu^I concentration {2-Br-BA (10 mM), $Cu[MeCN]_4PF_6$, NH_3 (0.0175 M), pH_{init} = 9.0}

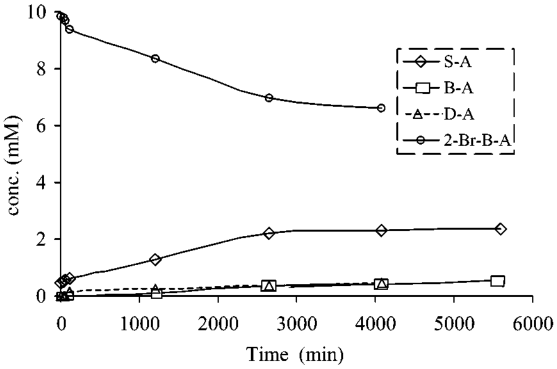


Figure 7. Kinetic traces of products and 2-Br-BA during the reaction of 2-Br-BA with Cu^+ monitored using HPLC [2-Br-BA (10 mM), $CuSO_4$ (1 mM) + Cu^0, pH_{init} = 6.0]

pH Changes During the Process

Short-Term pH Changes

In recording the pH changes after the addition of Cu^I (salt or solution with acetonitrile as stabilizing ligand) to an acidic solution of 2-Br-BA (pH = 3−5) we observed an initial increase in pH over several 100 s (Figure 8) followed

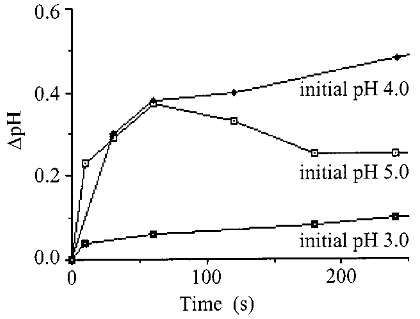


Figure 8. pH changes during the fast time scale of the reaction of 2-Br-BA with Cu^+ {2-Br-BA (10 mM), $Cu[MeCN]_4PF_6$ (1 mM)}

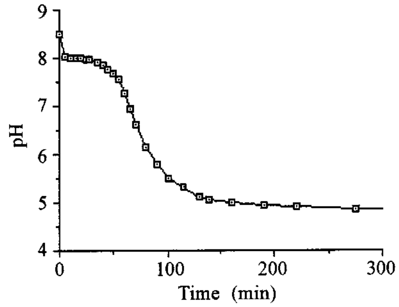


Figure 9. pH changes during the longer time scale of the reaction of 2-Br-BA with Cu^+ [2-Br-BA (10 mM), $CuSO_4$ (1 mM) + Cu^0]

by a slow decrease (Figure 9). The initial effect at pH = 3 was smaller than that for higher initial pH values, probably due to the buffer effect of 2-Br-BA ($pK_a = 2.8$).[5] Cu^I did not cause similar initial pH changes in the absence of 2-Br-BA, and we would rather expect an increase in acidity due to the addition of a metal salt to an aqueous solution. Furthermore, protons are released during the reaction of 2-Br-BA to form salicylic acid, see Equation (3), as was observed for longer reaction times.

$$\text{2-Br-BA} + H_2O\,[+\,Cu^+] \rightarrow \text{SA} + H^+ + \text{Br} \tag{3}$$

The initial increase in pH occurred over the same time span as the formation of the intermediate with the absorption around 350 nm, which was verified by simultaneous pH and UV/Vis measurements (employing fiber optics).

The increase in pH might in principle be due to an increase in the pK_a of the aromatic acid. Bonding of Cu^I to the aromatic ring (σ-donation from the HOMO of the π-system to Cu^I and π-back donation from Cu^I to the LUMO of the π-system) could cause such a change in pK_a. Indeed, excitation of aromatic acids induces a similar pK_a shift.[6] Assigning the intermediate with the absorption around 350 nm to a π-complex between Cu^I and 2-Br-BA poses several problems; no analogous complexes and no pH changes were detected when 2-Br-BA was replaced with benzoic acid. Furthermore, one expects that a complex formation of this kind should occur within a much shorter time. Alternatively, the formation of an intermediate with a σ-bond between the copper ion and a carbon atom of the aromatic ring (vide infra), might decrease the Cu^I−hydroxide interaction ($K_{sp} = 1\cdot10^{-14}\ M^2$),[5] see Equation (4) where $R^\cdot$ is an aryl radical.

$$L_nCu^IOH + R^\cdot \rightarrow Cu^{II}{-}R + n\,L + OH^- \tag{4}$$

We investigated the effect of pH on the life time of the intermediate and found that the decay of the absorption at 350 nm was faster at lower pH values. Whereas the intermediate had a life time of a couple of 100 s at pH = 5−7 it seemed to be stable for more than 1 h at pH = 9.

Long-Term pH Changes

Over longer time scales (several 100 min) the pH of the Cu^I/2-Br-BA system dropped from the initial value (5−9) to 4.6. An example is shown in Figure 9. A titration pointed out that the yield of H_3O^+ equaled the yield of salicylic acid, as expected according to Equation (3).

Experiments were performed where the pH was kept constant by dropwise addition of 0.10 N NaOH or NH_3 during the reaction under argon (the reaction was monitored spectrophotometrically by using fiber optics). In both those experiments, more salicylic acid was produced than in parallel experiments without the addition of extra base. The yields were highest for the system with NH_3 addition.

When the system reached pH ≤ 4.7 a black precipitate formed on the Cu metal. The precipitate could be dissolved in a basic solution. According to the resulting spectrum and elemental analysis, this precipitate consisted of Br^- and Cu ions. No Cu ions remained in the reaction mixture after extraction of the covered Cu metal plate. Taking into account the fact that the relative yield of Cu/bromine was 1:1, by titrating the amount of dissolved Br (Vollhardt) and weighing the Cu plate before and after the reaction, we could conclude that nearly complete comproportionation took place. For example, 0.18 mM of Br^- was precipitated from an initial reaction solution containing 0.10 mM of Cu^{2+} (0.20 mM would have been expected for full comproportionation). A similar precipitate was also formed in experiments with 2-Cl-BA. According to the literature, such precipitates consist of mixed-valence Cu^I and Cu^{II} halides, e.g. $(CuBr)_n(CuBr_2)_m$.[7a,7b]

Influence of the Cu^{2+} Concentration on the Product Distribution

Figure 10 shows the dependence of the product distribution (measured after 24 h) on the initial Cu^{2+} concentration. Increasing the Cu^{2+} concentration favored the formation of salicylic acid on account of the dimer concentration. The effect on the yield of benzoic acid is negligible.

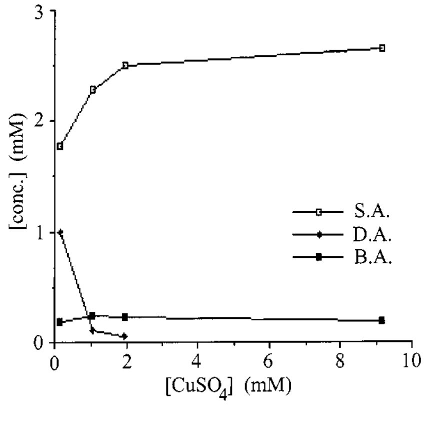


Figure 10. Dependence of the product distribution of the reaction of 2-Br-BA with Cu^+ (measured after 24 h) on the initial Cu^{2+} concentration [2-Br-BA (9 mM), Cu^I (2 mM) 5% MeCN, pH_{init} = 6.0]

ESR Measurements

In order to monitor the Cu^{2+} concentration during the reaction ESR spectroscopy was employed. Cu^{2+} (d^9) has an unpaired electron that makes it optimal for ESR studies, whereas Cu^I is ESR-silent (d^{10} system). A system containing Cu^I derived from comproportionation of Cu^{II} and Cu^0 metal in 4% CH_3CN did not produce an ESR signal, whereas a signal developed on addition of 2-Br-BA (g_{iso} = 2.16, see A and B in Figure 11). The final spectrum differs from that of Cu^{2+} with acetonitrile in aqueous solution and also from that of Cu^{2+} with 2-Br-BA (see A in Figure 12), but is very similar to that of Cu^{2+} with salicylic acid (see B in Figure 12).

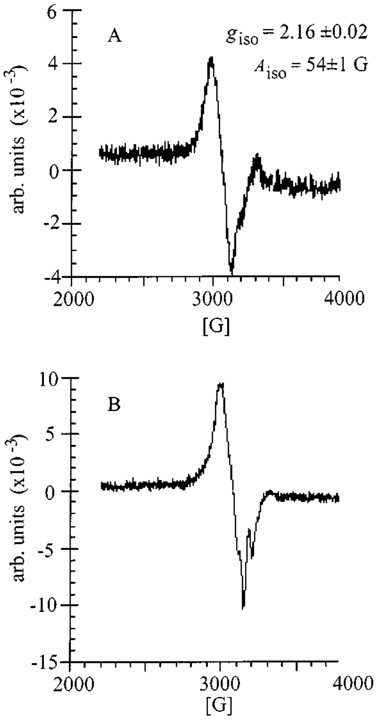


Figure 11. ESR spectra measured during the reaction of 2-Br-BA with Cu^+; A: after 120 s; B: after 24 h [2-Br-BA (10 mM), Cu^I (10 mM), 4% MeCN]

Figure 13 shows a typical kinetic trace of the formation of the ESR signal in the Cu^I/2-Br-BA system. Under the experimental conditions necessary for the ESR measurements (relatively high concentrations of the reactants) most of the Cu^{2+} would have formed during the 8−10 min needed before the first measurement could be performed. Comparing the kinetics and form of the ESR signal with that of the Cu^{2+}/salicylic acid system it becomes obvious that the produced Cu^{2+} forms a complex with salicylic acid created during the reaction. The initial ESR spectrum (see A in Figure 11) differs slightly from the final spectrum, raising the possibility that initially Cu^{II} forms a complex with the intermediate. Unfortunately, ESR spectra taken at low temperatures could not assist in clarifying this assumption.

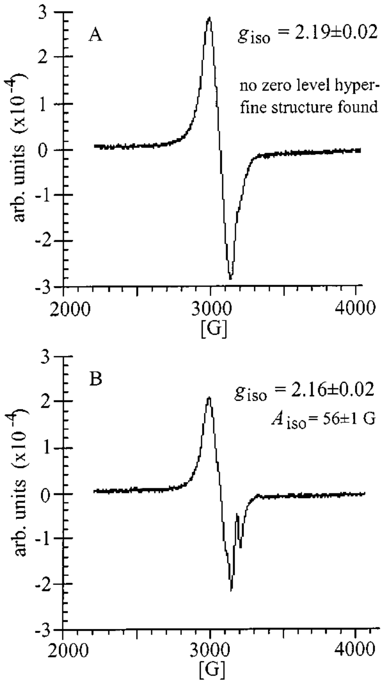


Figure 12. ESR spectra; A: 2-Br-BA (10 mM) with $CuSO_4$ (10 mM); B: SA (10 mM) with $CuSO_4$ (10 mM)

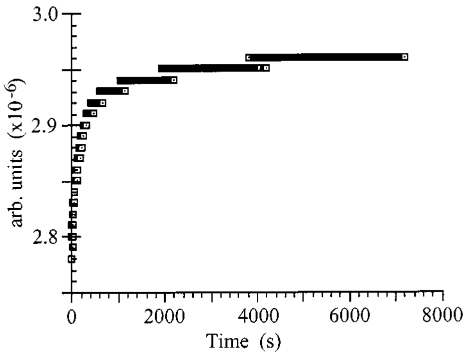


Figure 13. Time trace of ESR signal production due to Cu^{II} during the reaction of 2-Br-BA with Cu^+ [2-Br-BA (10 mM), Cu^I (10 mM), 2% MeCN (* 0-time is 8 min after mixing of the reactants, due to technical reasons)]

Influence of Different Ligands

The influence of different Cu^I-stabilizing ligands on the kinetics of the reaction was investigated.

Acetonitrile

A series of experiments in which Cu^I was formed by comproportionation under exclusion of dioxygen were performed for different concentrations of acetonitrile. The resulting Cu^I solutions were injected into solutions containing 2-Br-BA (under He). Figure 14 shows the change in absorbance due to SA formation at 296 nm (the absorbances were calculated from measurements in diluted solutions) after 2000 s as a plot of the CH_3CN percentage. For CH_3CN concentrations smaller than 4% the comproportionation was incomplete, causing an increase in the formation of salicylic acid until about 4% CH_3CN. For concentrations > 4% CH_3CN there was a definite decrease in SA formation.

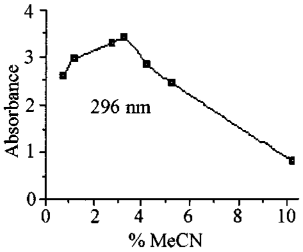


Figure 14. Change in absorbance due to SA formation at 296 nm after 2000 s as a plot of the CH_3CN percentage (the absorbances were calculated from measurements in diluted solutions) [2-Br-BA (25 mM), $CuSO_4$ (0.5 mM), Cu^0, MeCN, $pH_{init} = 9$]

In a similar experiment the formation of all organic products was investigated by HPLC (Figure 15). A decrease in the yield of all products with increasing CH_3CN concentration was observed. The influence on all the products is similar, therefore it is conceivable that CH_3CN plays a role in the first step of the reaction sequence.

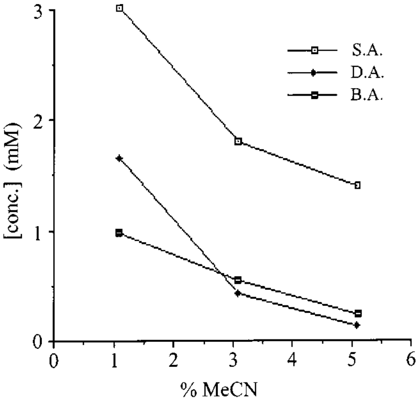


Figure 15. Changes in product distribution as a function of the CH_3CN percentage (the concentrations were determined after 24 h by HPLC) [2-Br-BA (10 mM), $CuSO_4$ (1 mM), Cu^0, MeCN, $pH_{init} = 6$]

Ammonia

NH_3 plays a major role in the formation of products. Its role cannot be explained solely by its stabilizing effect, as the reaction was also influenced at pH < 7, where NH_3 does not stabilize Cu^I anymore. A plot of the resulting absorbance at 296 nm vs. the concentration of NH_3 shows a similar pattern of increase and decrease of SA as for acetonitrile. At concentrations > 175 mM of NH_3 the formation of *o*-aminobenzoic acid was observed (verified by its absorbance at 318 nm, see Figure 1) in addition to the main product, SA.

Reaction with *o*-Chlorobenzoic Acid (2-Cl-BA)

In order to understand the influence of bromine, several parallel reactions with 2-Cl-BA instead of 2-Br-BA were studied. These reactions are considerably slower, but they seemed to follow a similar pathway.

Discussion

The above results for the Cu^I-catalyzed reaction of 2-Br-BA can be summarized by the following empirical observations:

1. As a first step an intermediate was formed with an absorbance in the 290−400 nm region. Transient complexes with copper−carbon σ-bonds[8a−8e] as well as d-π complexes of Cu^I [8d,9] with aromatic compounds are known to absorb in this wavelength region. For acidic starting pH values the pH initially rose during the formation of this intermediate. At acidic pH values (pH = 5) the intermediate was less stable than at basic pH values (pH = 9).

2. Several overlying reactions were observed at 296 nm, the absorption maximum of salicylic acid. The process can be divided into two time ranges so that the initial fast reaction covers the time when the concentration of the intermediate is relatively high.

3. During the fast time range the rate of reaction is linearly dependent on the 2-Br-BA concentration and quadratically dependent on the Cu^I concentration, implying the involvement of two Cu^I ions in the catalytic cycle.

4. During the reaction, Cu^{II} was formed, and most of it, according to the ESR measurements, during the initial phase. The ESR spectra of the final products indicate that most of the Cu^{II} is bound to salicylic acid.

5. pH dependence: The yield of the main product, salicylic acid, is considerably higher at basic pH than at acidic pH. The pH shifts during the reaction towards acidic pH and levels at pH ≈ 4.5. The proton yield stoichiometrically (1:1) equals the amount of salicylic acid formed. At pH = 4.5 a black precipitate, identified as $(CuBr)_n(CuBr_2)_m$,[7a,7b] forms and terminated the reaction. At pH values > 5 Cu^I apparently forms stronger complexes with the aromatic compounds.[3]

6. Excess Cu^{II} caused a relative decrease in the yield of the dimer and scarcely influenced the relative yields of salicylic and benzoic acids.

7. Influence of acetonitrile: Concentrations of more than 4% acetonitrile reduce the rate of formation of salicylic acid. For concentrations smaller than 3% the comproportionation was not yet complete, and therefore an increase in product formation was observed. Acetonitrile formed a complex with Cu^I and consequently was found to compete with 2-Br-BA for the Cu^I. At high acetonitrile concentrations the 2-Br-BA thus did not form the π-complex with 2-Br-BA. Alternatively, the formation of $Cu(CH_3CN)_n^+$ ($1 \leq n \leq 4$) shifted the redox potential of Cu^I anodically, leading to diminished reactivity.

8. Influence of ammonia: Similar to acetonitrile, ammonia also led to an increase in product formation at lower ammonia concentration, but to a decrease in rate at higher concentrations. Ammonia acted as a basic buffer and prevented the Cu^I ions from precipitating. Moreover, it formed

a σ-complex with Cu^I and thus changed its redox potential favorably, but a reaction of $Cu(NH_3)_2^+$ with a substrate requires a hybridization change probably from sp to sp^3. Such a hybridization change is endothermic and was recently shown to decrease the rate of reaction of Cu^I with $CCl_3CO_2^-$.[10]

9. The aromatic substrate, 2-Br-BA, induced comproportionation and catalyzed the formation of Cu^I by formation of a π-complex of Cu^I with the aromatic compound, thus shifting the equilibrium of the reaction according to Equation (1) to the Cu^I side.[3]

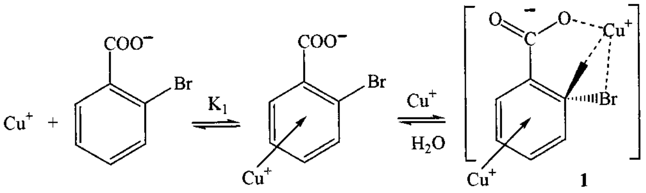
10. The isomers 3- and 4-Br-BA are considerably less reactive[1c,11,12] under the conditions used for the reaction of 2-Br-BA, implying that the interaction of Cu^I with Br as well as with the carboxylic substituent (chelate effect) is of importance.

11. A radical mechanism involving the Ar$^{\cdot}$ radical can be ruled out, as pulse radiolysis experiments (data not shown) point out that aryl radicals, produced in the presence of 2-Br-BA and Cu^I, reacted with the aromatic acid and not with Cu^I. The product of this reaction was the dimer bromodiphenoic acid, which is not a major product of the investigated catalytic process.

12. 2-Cl-BA reacted slower than 2-Br-BA, but otherwise followed the same pattern as discussed in the previous points, thus suggesting that the detachment of the halogen is the rate-determining step.

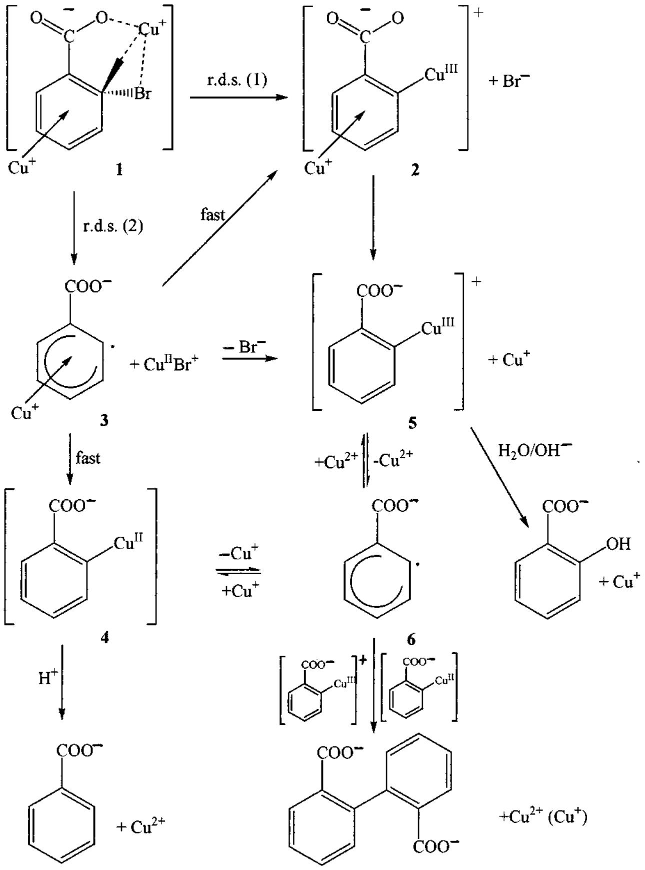
The Proposed Mechanism

The results are consistent with the following mechanism for the formation of the reactive intermediate (Scheme 2). First a Cu^I ion forms a d-π* complex with the aromatic ring of 2-Br-BA followed by the interaction of a second Cu^I ion with the Br and carboxylate substituents.



Scheme 2

The aromatic ring of the intermediate is probably distorted as the carbon atom, bearing the Br substituent, attains tetrahedral character, in agreement with previous proposals from the literature.[12a−12c] The coordination of the Cu^I ion to the aromatic ring probably distorts it and also lengthens the C−Br bond,[13a−13f] thus facilitating the abstraction of Br. The proposed follow-up reactions, which fit all the observed results are summed up in Scheme 3.



Scheme 3

The rate-determining step is obviously the bond breakage of the C−Br bond, as this step involves two Cu^I ions and therefore fits the second-order dependence on Cu^I, as was found experimentally. Moreover, this hypothesis is corroborated by the fact that 2-Cl-BA reacted in a similar manner to 2-Br-BA, only much slower.

The bond breakage of C−Br might follow two possible routes. In one a formal oxidation takes place to obtain intermediate **2** or **5**. In a second possibility, intermediate **3** is formed, which either reacts with the $Cu^{II}Br$ formed in a cage to yield intermediates **2** or **5**, or transforms immediately into intermediate **4**. Intermediates **2** and **5** can decompose by two different pathways. In the first the Cu−C bond breaks heterolytically to produce the main products of the reaction, salicylic acid, Cu^I, and a proton. On the other hand, intermediate **5** can decompose homolytically in a side reaction to form Cu^{II} and the radical **6**, which might dimerize to produce diphenoic acid. The radical **6** can also react with the intermediate **5** to produce the dimer and Cu^{II}, a termination step leading to loss of Cu^I. This reaction is more plausible as $[Cu^{III}C_6H_4CO_2^-] >> [C_6H_4CO_2^{\cdot -}]$. For high concentrations of Cu^{II} the equilibrium of the homolytic decomposition of intermediate **5** is shifted towards its formation and therefore less dimer is formed at high concentrations of Cu^{II}.

Intermediate **4** might decompose heterolytically, in an acid-catalyzed reaction, to form benzoic acid and Cu^{II}. This is a side reaction, in which Cu^{I} is removed from the reaction system stoichiometrically, and therefore the rate of the overall reaction (formation of salicylic acid) will slow down with time. Intermediate **4** can also react with the radical to form Cu^{I} and the dimer, in this pathway Cu^{I} is restored to the catalytic cycle. In addition, intermediate **4** can decompose homolytically and can thus be restored to the salicylic acid producing cycle.

According to the experimental observations, the reaction can be divided into at least two time scales. During the short time scale, seconds to minutes (depending on the relative concentrations of Cu^{I}, 2-Br-BA, initial pH, and initial Cu^{II} concentration), the intermediate is observed, as well as the increase in pH, second-order dependence on Cu^{I} and the yield of salicylic acid and the dimer are relatively high. At the same time, a rapid increase in Cu^{II} concentration is observed. During the slower phase, hours to days, a slow further increase in salicylic acid and a considerably slower increase in the dimer yield are observed; it seems that the rate of formation of benzoic acid is pH-dependent and thus its relative yield increases with time. The yield of Cu^{II} is especially low compared to the first phase. The absorption at 350 nm is nearly non-existent, and therefore the intermediate concentration as well as the Cu^{I} concentration are presumably low.

The origin of the two time scales is probably the fast formation of Cu^{II} on account of Cu^{I}. Cu^{II} is produced during the formation of the dimer and the benzoic acid. The dimer, which is formed mainly during the first time frame, when the steady-state concentrations of the intermediates **5**, **6**, and **4** are relatively high, is responsible for the majority of the Cu^{II} formed, later its formation is hindered by high Cu^{II} concentration. The decrease in Cu^{I} concentration, which also stems from the formation of insoluble CuBr, causes a decrease in the concentration of the intermediate and slows down the reaction. Moreover, the pH, that decreases during the reaction slows down the process, and finally at pH = 4.7 and relatively high Cu^{II} concentrations the formation and precipitation of a mixed-valence compound stops the catalytic reaction as a result of removing the rest of Cu^{I} from the reaction system.

Concluding Remarks

This study proves that Cu^{I} species are the catalysts in the Ullmann reaction. Furthermore, the results clearly point out that the addition of ligands that stabilize Cu^{I} in aqueous solutions, beyond a given optional concentration, slow down the catalytic process. This observation is attributed to the effect of the ligands on the Cu^{II}/Cu^{I} redox potential and thus on the Cu^{I} reactivity. (The latter might also be affected by the binding mode of the Cu^{I} ion to the ligand.[10]) Therefore, the use of CH_3CN or alkenes as solvents for Cu^{I}-catalyzed reactions is not recommended.

Experimental Section

Materials: All solutions were prepared from reagent grade chemicals or better. Distilled water was further purified by passing through a Milli Q Millipore setup, final resistivity > 10 MΩ/cm. All experiments were carried out at room temperature (22±2 °C). Cu^{I} solutions were prepared by comproportionation of Cu^{II} solutions (usually $CuSO_4$) with Cu^{0} metal (activated by concentrated HNO_3). The solution was stirred for at least 24 h. All experiments involving Cu^{I} were carried out in strictly de-aerated solutions using the syringe technique and helium or argon gas. Aqueous solutions of the aromatic acids were prepared by completely dissolving the solids in basic solutions (NaOH) and acidifying to the desired pH by titration with $HClO_4$.

Techniques: The pH was measured with a Corning 220 or a Hanna (HI 9017) pH meter and adjusted with $HClO_4$ and/or NaOH.

UV/Vis: Spectra were recorded with a Hewlett Packard 8452A diode array spectrophotometer. Special cells for anaerobic studies were used. The concentration of Cu^{2+}(aq) and indirectly Cu^{+} (after oxidation to Cu^{2+} with atmospheric dioxygen) was determined spectrophotometrically by the addition of ammonia to form the complex $Cu(NH_3)_4{}^{2+}$, which has a molar absorption coefficient of 60 $\text{M}^{-1}\text{cm}^{-1}$ at 604 nm. Fast reactions were monitored by employing an SFA-11 Rapid Kinetics Accessory (Hi-Tech). In some cases, where pH and spectral measurements were performed simultaneously, fiber-optical connections by Phonetics were employed.

HPLC: Organic starting materials and products were separated and identified with the help of a Spectraphysics Analytic Inc. HPLC (SP Thermo Separation, A 0099-510) in conjunction with a Spectrophotometer, Spectra Series (p200) which operates in the 200−400 or 400−800 nm region (5 nm resolution). A Merck 50942 LiChroCart 125-4, LiChrospher 100 RP-8 (5 µm) column was utilized. A mixture of 35% MeCN (HPLC grade) and 65% 0.05 M phosphate buffer at pH = 3.5 was used as the eluent at a rate of 0.3 mL/min; chromatograms were thus collected within 10 min. Calibrations for starting materials and possible products were performed at 220, 260, and 295 nm (area of peaks) if applicable.

ESR: Spectra were recorded with a Bruker EMX 220 X-band ESR spectrometer. The different complexes of Cu^{II} with the aromatic compounds could be identified at 120 K. In some instances kinetics were measured at room temp. by using air-tight ESR tubes.

NMR: Spectra were recorded with a Bruker DPX 200 MHz. $Cu(CH_3CN)_4PF_6$ was used as a source of Cu^{I}, dissolved in 3% CH_3CN/D_2O.

Acknowledgments

This study was supported in part by a grant from the Budgeting and Planning Committee of The Council of Higher Education and the Israel Atomic Energy Commission. D. M. wishes to express his thanks to Mrs. Irene Evens for her ongoing interest and support.

[1] [1a] F. Ullmann, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853. [1b] A. A. Moroz, M. S. Shvartsberg, *Russ. Chem. Rev.* **1974**, *8*, 43. [1c] Kirk-Othmer, *Encyclopedia of Chemical Technology* (Th. 3), Wiley, New York, **1978**, vol. 8, p. 276.

[2] F. A. Cotton, G. Wilkinson, *Advanced Inorganic Chemistry*, 5th ed., Wiley Interscience, New York, **1988**, pp. 757−758.

[3] M. Saphier, A. Burg, S. Sheps, H. Cohen, D. Meyerstein, *J. Chem. Soc., Dalton Trans.* **1999**, 1845.
[4] A. J. Parker, *Search* **1973**, *4*, 426.
[5] J. A. Dean, *Lange's Handbook of Chemistry*, 14th ed. McGraw-Hill, Inc., New York, **1992**, Table 8.6.
[6] P. Day, *Endeavour* **1970**, *29*, 45.
[7] [7a] F. A. Hart, J. Newbery, P. Thornton, *Annu. Rep. Prog. Chem. Sect. A* **1980**, *77*, 232. [7b] C. J. Brown, P. J. McCarthy, I. D. Salter, *J. Organomet. Chem.* **1990**, *394*, 711.
[8] [8a] H. Cohen, D. Meyerstein, *Inorg. Chem.* **1987**, *26*, 2342. [8b] H. Cohen, D. Meyerstein, *Inorg. Chem.* **1986**, *25*, 1506. [8c] M. Masarwa, H. Cohen, D. Meyerstein, *Inorg. Chem.* **1991**, *30*, 1849. [8d] S. Goldstein, G. Czapski, H. Cohen, D. Meyerstein, *Inorg. Chim. Acta* **1992**, *192*, 87. [8e] D. Meyerstein, *Inorg. Chem.* **1975**, *14*, 1716.
[9] H. Cohen, D. Meyerstein, *Inorg. Chem.* **1986**, *25*, 1505.
[10] N. Navon, H. Cohen, D. Meyerstein, *Inorg. Chem.* **1997**, *36*, 3781.
[11] A. Bruggink, A. McKillop, *Tetrahedron* **1975**, *31*, 2607.
[12] [12a] B. Liedholm, *Acta Chem. Scand.* **1969**, *23*, 3175. [12b] B. Liedholm, *Acta Chem. Scand.* **1971**, *25*, 106. [12c] B. Liedholm, *Acta Chem. Scand.* **1976**, *30*, 141.
[13] [13a] R. W. Turner, E. L. Amma, *J. Am. Chem. Soc.* **1963**, *85*, 4046. [13b] R. W. Turner, E. L. Amma, *J. Am. Chem. Soc.* **1966**, *88*, 1877. [13c] H. Schmidbaur, W. Bublak, B. Huber, G. Reber, G. Muller, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1089. [13d] C. J. Brown, *J. Organomet. Chem.* **1990**, *394*, 711. [13e] P. J. McCarthy, *J. Chem. Soc., Chem. Commun.* **1989**, 395. [13f] G. B. Ansell, *Acta Crystallogr., Sect. C* **1984**, *40*, 365.

Received October 24, 2001
[I01419]