Cu(I)(2,5,8,11-tetramethyl-2,5,8,11-tetraazadodecane)$^+$ as a catalyst for Ullmann's reaction †

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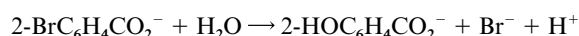[a] *Chemistry Department, Ben-Gurion University of the Negev, Beer-Sheva, Israel*
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Cu(I)L complexes catalyze the Ullmann reaction

$$2\text{-BrC}_6\text{H}_4\text{CO}_2^- + \text{H}_2\text{O} \longrightarrow 2\text{-HOC}_6\text{H}_4\text{CO}_2^- + \text{Br}^- + \text{H}^+$$

however the process is slow and undesirable yields of benzoic acid and diphenoic acid are formed. The optimal ligand, L, for this catalyst should enhance the rate of the process, probably *via* shifting the redox potential of the Cu(II/I) couple cathodically, inhibit the formation of the diphenoic acid, probably *via* steric hindrance, and of benzoic acid probably *via* buffering the solution at pH > 7. The results demonstrate that Cu(I)(2,5,8,11-tetramethyl-2,5,8,11-tetraazadodecane)$^+$, *i.e.* Cu(I) with a ligand which fulfils these requirements, is a very good catalyst for this process with a selectivity of > 97% and high turnover numbers.

Introduction

It is well known that Cu(I) species catalyze the Ullmann reaction[1–6] and specifically the transformation of 2-bromobenzoic acid into salicylic acid with benzoic acid and diphenoic acid as side products, Scheme 1. A detailed recent mechanistic study[3] suggested that the mechanism of this process involves the reactions shown in Scheme 2.


Scheme 1
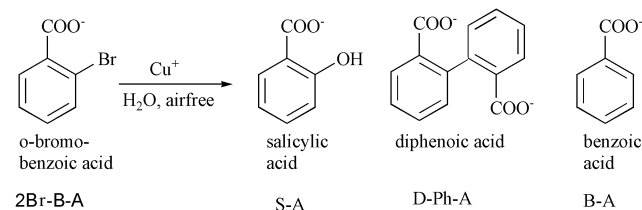
Thus in order to optimize the catalytic process one has to: (1) Increase the concentration of Cu(I) species in the system; in aqueous solutions this means to use a ligand which prevents the precipitation of CuOH or Cu$_2$O,[7] and the disproportionation of Cu$^+$ (aq).[7] (2) Cathodically shift the redox potential of the Cu(II/I)L couple relative to the Cu$^{2+/+}$ (aq) couple (to increase the rate of the process).[8] (3) Use a ligand which will impose sufficient steric hindrance to inhibit the formation of diphenoic acid (which is formed *via* the reaction of intermediate **6** with intermediate **5**, or **4** in Scheme 2). (4) Decrease the yield of benzoic acid; the ligand should enable maintainence of a pH of > 7, thus decreasing the rate of formation of benzoic acid *via* the reaction of intermediate **4** with H$^+$, Scheme 2. Intermediate **4** might also react with water to yield benzoic acid, this reaction clearly cannot be inhibited in aqueous solutions.

These considerations led us to study the properties of Cu^{I}L$^+$, L = 2,5,8,11-tetramethyl-2,5,8,11-tetraazadodecane, as a catalyst for this process as it is known that: (1) The redox potential of the Cu(II/I)L couple is 12 mV at pH 10.0,[9] *i.e.* it is shifted cathodically relative to the Cu$^{2+/+}$ (aq) couple. (2) This ligand induces considerable steric hindrance around the central copper ion. (3) As the pK_as of this ligand are pK_{a1} = 9.23, pK_{a2} = 8.47, pK_{a3} = 5.36 and pK_{a4} = 1.68[8] it is a relatively good buffer at pH > 7.

Scheme 2
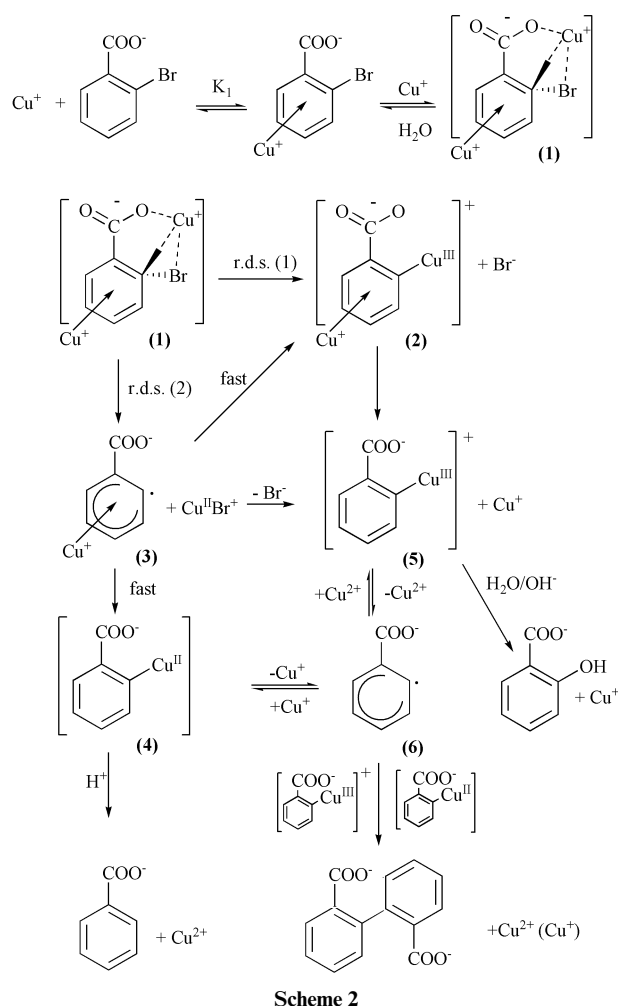
The results indeed point out that Cu^{I}L$^+$ is a good catalyst for this process.
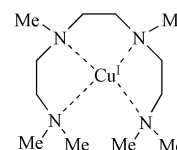
Results

Mixing of a solution containing $2\text{-}BrC_6H_4CO_2^-$ with a solution containing CuL^+ at pH 10.0 in the stopped-flow resulted in two observations: (1) An immediate increase in the absorption at 320 nm, on a time scale faster than the mixing time. This rise is proportional to $[2\text{-}BrC_6H_4CO_2^-]$, indicating the fast formation of an intermediate *via* the reaction of Cu^IL^+ with $2\text{-}BrC_6H_4CO_2^-$. (2) A slower reaction with a rate proportional to $[Cu^IL^+]$. However, this process is observed also when Cu^IL^+ is mixed with H_2O at pH 10.0, *i.e.* in the absence $2\text{-}BrC_6$-$H_4CO_2^-$. It is concluded that the reaction observed is due to some O_2 which penetrates the system during the mixing time. After the reaction with O_2 is over no fast process is observed.

These experiments point out that although an intermediate is formed *via* a fast reaction between Cu^IL^+ and $2\text{-}BrC_6H_4CO_2^-$ the formation of salicylic acid is slow and almost unobserved over the first 1000 seconds. On the other hand the penetration of some O_2 during the mixing cannot be avoided under our experimental conditions. Therefore it was decided to prepare Cu^IL^+ *in situ via* comproportionation of $Cu^{II}L^{2+}$ and Cu^0 in the presence of excess L and follow the kinetics by measuring the yield of the organic products using HPLC.

The effect of the addition of L on the rate of the process and the composition of the products is illustrated in Fig. 1.
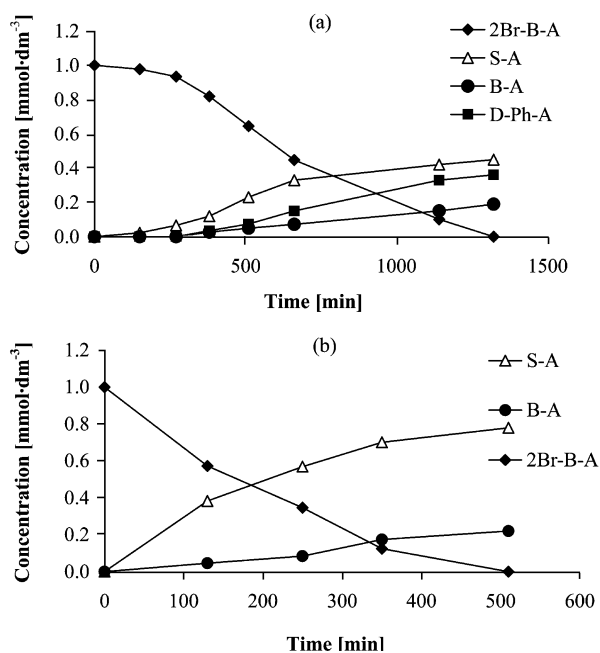

Fig. 1 The effect of the addition of L on the rate of the process and composition of the products. (a) 2-Bromobenzoic acid (1 mmol dm^{-3}), CuSO$_4$ (0.025 mmol dm^{-3}), Cu^0, pH = 7.0, T = 25 °C. (b) 2-Bromobenzoic acid (1 mmol dm^{-3}), CuSO$_4$ (0.025 mmol dm^{-3}), L (0.125 mmol dm^{-3}), Cu^0, pH = 7.0, T = 25 °C.

The results clearly demonstrate that addition of the ligand: (1) Accelerates considerably the rate of the process and shortens the induction time. (2) Inhibits the formation of diphenoic acid. (3) Increases the yield of salicylic acid.

Thus it is clear that the addition of L is beneficial and therefore experiments to optimize the process were performed.

The effect of the substrate, $2\text{-}BrC_6H_4CO_2^-$, concentration on the rate of the process and the product selectivity is plotted in Fig. 2.

The results clearly demonstrate that the rate of the process accelerates considerably with $[2\text{-}BrC_6H_4CO_2^-]$ whereas the selectivity decreases. The final pH of the solution also decreases with the increase in $[2\text{-}BrC_6H_4CO_2^-]$ being 8.4; 7.5 and 4.8 for $[2\text{-}BrC_6H_4CO_2^-]$ = 0.25; 0.50 and 1.0 mmol dm^{-3}, respectively.

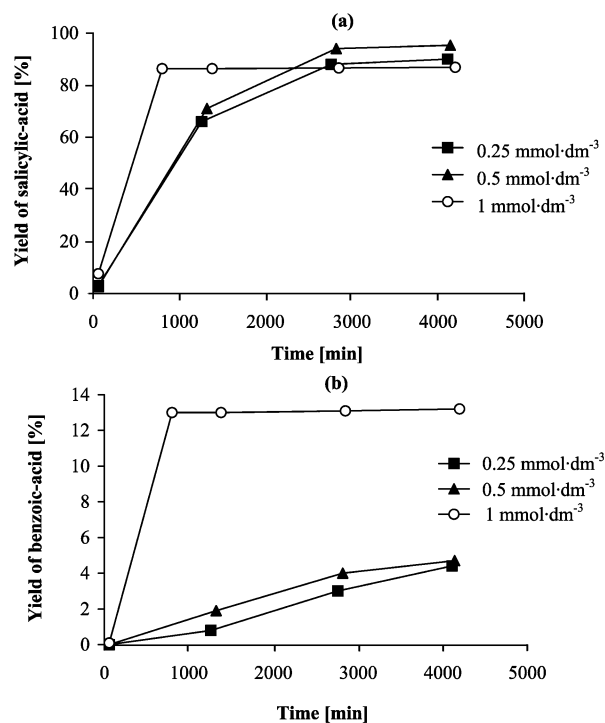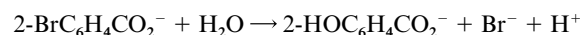**Fig. 2** The effect of the substrate, $2\text{-}BrC_6H_4CO_2^-$, concentration on the rate of the process and the selectivity. (a) and (b): 2-bromobenzoic acid, CuSO$_4$ (0.025 mmol dm^{-3}), L (0.125 mmol dm^{-3}), Cu^0, pH = 10.0, T = 25 °C.

This result is in accord with the expectation for the main reaction:

$$2\text{-}BrC_6H_4CO_2^- + H_2O \longrightarrow 2\text{-}HOC_6H_4CO_2^- + Br^- + H^+$$

The increases in the yield of $C_6H_5CO_2^-$ are in accord with expectations according to the mechanism summed up in Scheme 2. Indeed analysis of Fig. 2 indicates that most of the $C_6H_5CO_2^-$ is formed towards the end of the process, *i.e.* at lower pHs. This is even better demonstrated when one compares the results for solutions with an initial pH of 10.0, Fig. 2, with those with an initial pH of 7.0, Fig. 1, where the yield of $2\text{-}HOC_6H_4CO_2^-$ is 86.8 and 77.9%, respectively whereas the yield of $C_6H_5CO_2^-$ is 13.2 and 22.1%, respectively.

These results suggest that the process can be improved by raising the pH and/or by adding a buffer; for pH 10 a 0.125 M borax buffer was chosen. The effect of pH on the rate of the process is plotted in Fig. 3. Surprisingly the results point out that the rate of the process decreases with the increase of pH though the selectivity of the process increases. This result suggests that OH$^-$ or the borate anion act as additional ligands
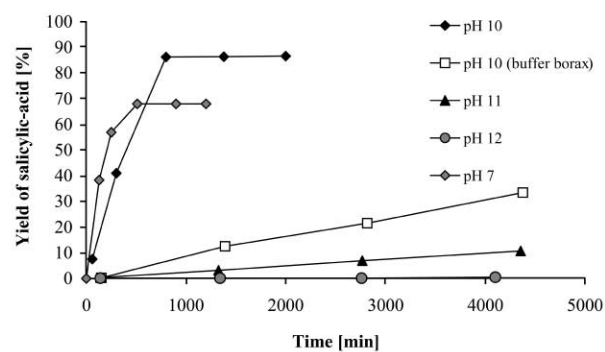

Fig. 3 The effect of pH on the rate of the process. 2-Bromobenzoic acid (1 mmol dm^{-3}), CuSO$_4$ (0.025 mmol dm^{-3}), L (0.125 mmol dm^{-3}), Cu^0, T = 25 °C.

to Cu^IL^+ thus slowing down the process. Alternatively the pH effect on the rate of the process might be due to its effect on the rate of the comproportionation reaction, see below.

Alternatively the ligand L can be used as a buffer. Therefore the effect of its concentration on the rate of the process was studied, the results are summarized in Fig. 4, the final pH values are given in the figure. The concentrations of copper ions at the end of the process were measured by aerating aliquots, thus oxidizing the C^IL^+ to $Cu^{II}L^{2+}$, and measuring the concentration of $Cu^{II}L^{2+}$ by measuring the OD at 666 nm . The results highlight that $[Cu^{II}L^{2+}]$ is independent of [L], i.e. the effect of [L] on the rate of the process is not due to an effect on $[Cu^IL^+]$.
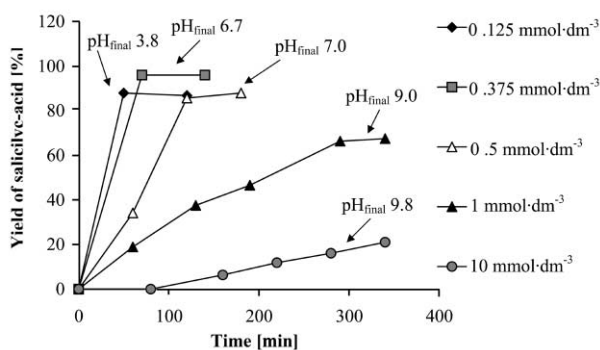

Fig. 4 The effect of ligand concentration on the rate of the process. 2-Bromobenzoic acid (1 mmol dm^{-3}), CuSO$_4$ (0.025 mmol dm^{-3}), pH = 10.0, T = 60 °C.

The results clearly demonstrate that the rate of the process decreases with the increase in [L] though the selectivity increases. The results suggest that L = 0.375 mmol dm^{-3} is the optimal concentration for $[Cu^{2+} (aq)]_0$ = 0.025 mmol dm^{-3}. Under these conditions, at pH$_0$ = 10.0 the yield of 2-HOC$_6$H$_4$CO$_2^-$ is 96%.

The effect of the concentration of Cu^IL^+, $[Cu^IL^+]$ = $2[Cu^{II}L^{2+}]_0$, was studied, the results are plotted in Fig. 5. The results clearly demonstrate that the rate of the process increases linearly with $[Cu^IL^+]$. Thus the results demonstrate that the initiation step differs for Cu^IL^+ and $Cu^I(CH_3CN)_n^+$ where it depends linearly on $[Cu^I(CH_3CN)_n^+]^2$.[3]
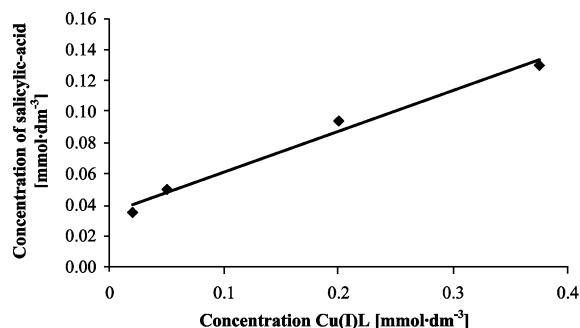

Fig. 5 The effect of the concentration of Cu^IL^+. 2-Bromobenzoic acid (1 mmol dm^{-3}), CuSO$_4$, L (0.375 mmol dm^{-3}), Cu^0, pH = 10.0, T = 25 °C. The yield were measured after 4 hours, i.e. after the comproportionation reaction was completely finished.

The apparent activation energy of the process was determined by measuring the yield of 2-HOC$_6$H$_4$CO$_2^-$ 30 min after the beginning of the process and calculating the initial rate constant from these yields. The results are summarized in Fig. 6, from which E_a(apparent) = 81 ± 5 kJ mol^{-1} is derived.

The results thus suggest that one could obtain larger yields of 2-HOC$_6$H$_4$CO$_2^-$ if one starts with higher initial concentrations of 2-BrC$_6$H$_4$CO$_2^-$ and maintains a constant pH throughout the process. This was performed by starting with 10 mmol dm^{-3} 2-BrC$_6$H$_4$CO$_2^-$ and continuously bubbling He through the
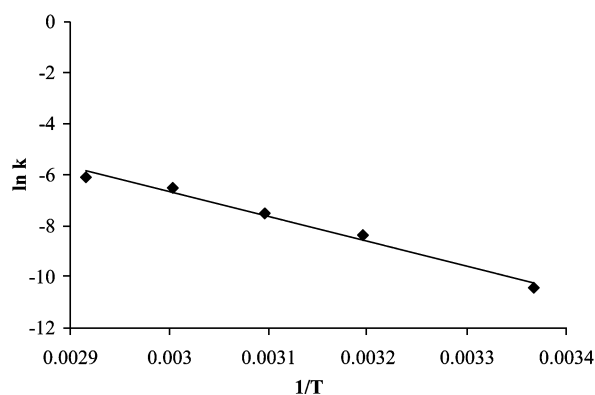

Fig. 6 Determining the apparent activation energy of the process. 2-Bromobenzoic acid (1 mmol dm^{-3}), CuSO$_4$ (0.025 mmol dm^{-3}), L (0.375 mmol dm^{-3}), Cu^0, pH = 10.0.

solution and titrating with deaerated 0.1 M NaOH to maintain constant pH. These experiments were performed at pH 9.0, Figs. 7 and 8, and at pH 10.0. The results demonstrate that the process is considerably faster at pH 9.0, Fig. 8, though the selectivity of the 2-HOC$_6$H$_4$CO$_2^-$ yield, 96.8%, is slightly lower than at pH 10.0, 97.5%.
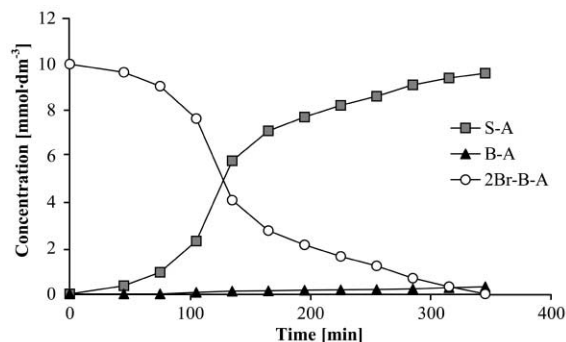

Fig. 7 2-Bromobenzoic acid (10 mmol dm^{-3}), CuSO$_4$ (0.025 mmol dm^{-3}), L (0.375 mmol dm^{-3}), Cu^0, pH = 9.0, T = 60 °C.
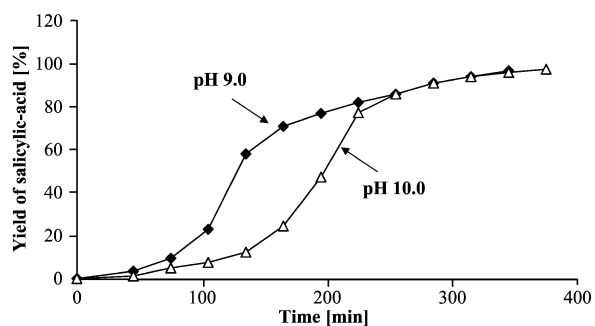

Fig. 8 2-Bromobenzoic acid (10 mmol dm^{-3}), CuSO$_4$ (0.025 mmol dm^{-3}), L (0.375 mmol dm^{-3}), Cu^0, T = 60 °C.

The results presented in Fig. 8 suggest a relatively long initiation period. This could be due to the rate of the comproportionation reaction. The latter was measured by following the OD at 284 nm of solutions containing $Cu^{II}L^{2+}$, L and Cu^0. This wavelength was chosen because at this point $\varepsilon(Cu^{II}L^{2+}) > \varepsilon(Cu^IL^+)$. The results are plotted in Fig. 9. The results clearly demonstrate that the comproportionation reaction is considerably faster at pH 9.0. However the rate is considerably higher than that predicted from the observed initiation period, Fig. 8.

One source for the difference might be the absorbance of the aromatic acid to the Cu^0 surface. In order to check this possibility the effect of C$_6$H$_4$CO$_2^-$ on the rate of the comproportionation reaction was measured, Fig. 10. The results clearly demonstrate that the aromatic acids indeed slow down the comproportionation process.
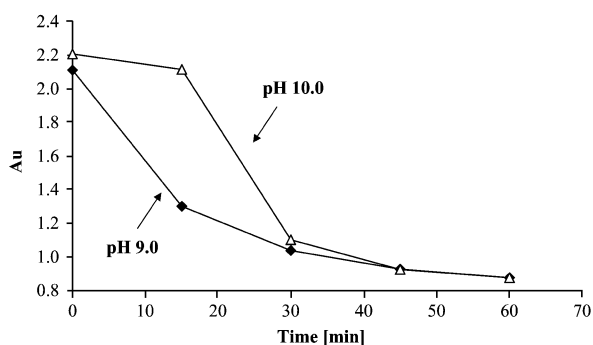
Fig. 9 Dependence of the rate of the comproportionation reaction on pH. $CuSO_4$ (0.3 mmol dm^{-3}), L (1.5 mmol dm^{-3}), Cu^0, $T = 60$ °C, $\lambda = 284$ nm.
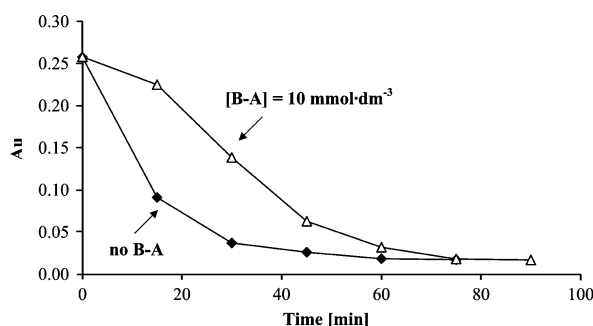

Fig. 10 Effect of the aromatic acid on the rate of the comproportionation process. $CuSO_4$ (1.5 mmol dm^{-3}), L (7.5 mmol dm^{-3}), Cu^0, pH = 10.0, $T = 60$ °C, $\lambda = 646$ nm.

Discussion

The results clearly demonstrate that the addition of the ligand L to the reaction mixture containing Cu^{2+}, Cu^+, Cu^0 and 2-$BrC_6H_4CO_2^-$ improves the catalytic process. This improvement is three-fold: (1) The addition of the ligand accelerates the catalytic process, probably by increasing the concentration of the Cu^I species in the system and by increasing the rate of the bromide abstraction from 2-$BrC_6H_4CO_2^-$, see below. (2) The addition of the ligand enables high turnovers when one maintains a constant pH. (3) The addition of the ligand improves the selectivity of the process. The yield of 2-$HOC_6H_4CO_2^-$ is increased to *ca.* 97% as compared to 45% in its absence. Furthermore in the presence of the ligand the formation of diphenoic acid is totally inhibited. The latter result is probably due to the steric hindrance imposed by L, inhibiting the reaction:
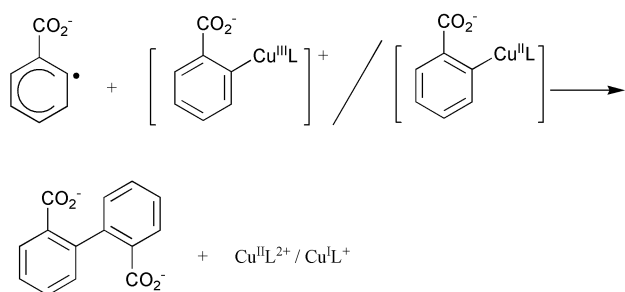

which is the source of diphenoic-acid, Scheme 2.[3]

The results further demonstrate that in the presence of L the process is first order in [Cu^IL^+], after the comproportionation reaction is over, Fig. 5. This result differs from that observed when $Cu^I(CH_3CN)_n^+$ is used as a catalyst where the rate depends linearly in [$Cu^I(CH_3CN)_n$]^2.[3] This observation is attributed to the considerable cathodic shift of the Cu(II/I) couple when L replaces $(CH_3CN)_n$. Therefore one Cu^IL^+ only is
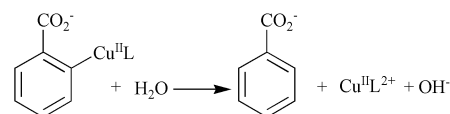
required to abstract a bromide from 2-$BrC_6H_4CO_2^-$ or to insert into the Br–C bond.

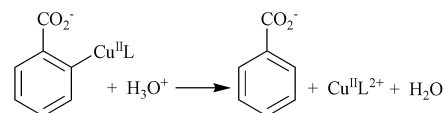The latter two observations require that Scheme 2 be replaced by Scheme 3 in the presence of the ligand L.
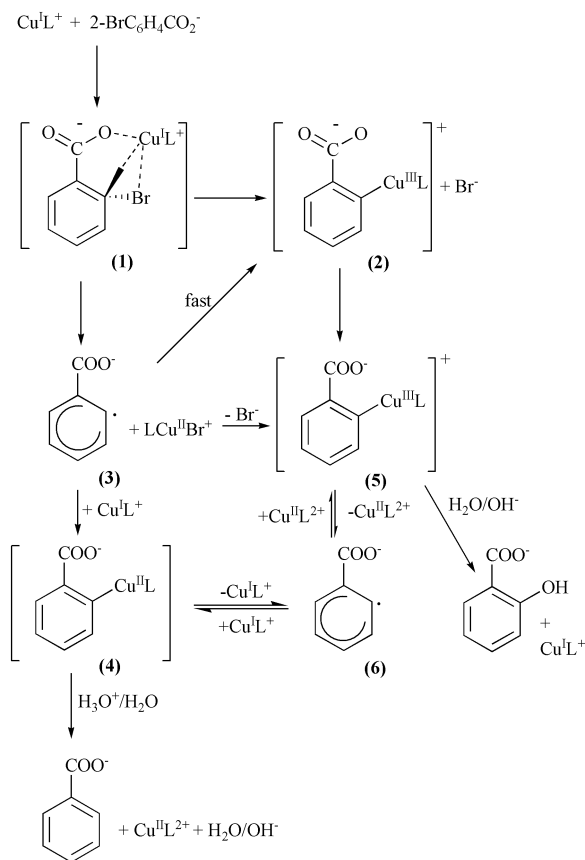
Scheme 3

The yield of $C_6H_5CO_2^-$ can be minimized by keeping the pH of the system above pH 8 throughout the process. The residual yield of benzoate, *ca.* 3%, is probably due to the reaction:

This reaction is expected to be considerably slower than the reaction:

As the heterolysis reactions of metal–carbon bonds in general[10–15] and Cu^{II}–carbon bonds specifically[16] are known to be acid catalyzed.

At high pHs or in the presence of excess ligands the process is slowed down. This observation stems probably from two sources: (1) The extra ligands slow down the comproportionation reaction either *via* adsorbtion to the surface of Cu^0 or by ligation to $Cu^{II}L^{2+}$ which stabilizes the Cu(II) oxidation state. (2) The formation of intermediate **1**, Scheme 3, probably requires that the Cu(I) center will be bound to L at most *via* three coordination sites, *i.e.* one of the terminal amines has to be released, this happens as an equilibrium process and it is known that the fourth amine is bound weakly to the copper.[9] The additional ligands, including OH^-, are expected to compete with 2-$BrC_6H_4CO_2^-$ for this coordination site.

It should be noted that under our experimental conditions the rate determining step, at least in the initiation phase of the process, is the comproportionation reaction.

Finally it is tempting to suggest that L, or analogous ligands, will be beneficial additives to other processes catalyzed by Cu(I) species, which do not require a large space in the vicinity of the central copper ion.

Experimental

Materials

All the chemicals used in this study were of A.R. grade, purchased from Aldrich and Merck. Solutions were prepared in distilled water which was further purified by passing through a Milli Q Millipore setup, final resistivity > 10 MΩ cm^{-1}. The ligand L was purchased from Aldrich. All solutions were strictly deaerated using the syringe technique and He gas. When deaerated solutions had to be mixed, a solution from one syringe was injected into a second syringe *via* a three way valve. Aqueous solutions of the aromatic acids were prepared by completely dissolving the solids in basic, NaOH solutions and acidifying to the desired pH by titration with HClO$_4$.

Cu^{I}L$^+$ was prepared by deaerating a solution containing 2-BrC$_6$H$_4$CO$_2^-$, L, CuSO$_4$ and then adding, during He bubbling, a Cu^0 strip which was first activated in concentrated HNO$_3$ and washed with water. In some experiments Cu^{I}L$^+$ was prepared in the absence of 2-BrC$_6$H$_4$CO$_2^-$ and then injected into a solution containing 2-BrC$_6$H$_4$CO$_2^-$.

Techniques

pH Measurement. The pH was measured with a Hanna (HI 9017) pH meter and adjusted with HClO$_4$ and/or NaOH as required.

UV/VIS Spectroscopy. Spectra were recorded with a Hewlett Packard 8452A diode array spectrophotometer.

Stopped-flow. The kinetics of reaction were investigated using an Applied Photophysics SX.18MV stopped flow system which measures rates of reaction in the time span 1–10^6 ms.

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 50943 LiChroCart 125–4, LiChrospher 100 RP-18 (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 0.5 ml min^{-1}; chromatograms were thus collected within 8 min. Calibration for starting materials and possible products were performed at 220, 260 and 295 nm (area of peaks) if applicable.

Determination of [Cu^{I}L$^+$] in the reaction mixture. Aliquots of the solution, not containing any Cu^0, were aerated and the concentration of Cu^{II}L^{2+} thus formed was determined at 666 nm where only the latter complex has an absorption band.

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