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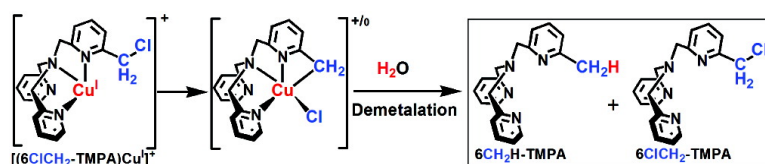
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Suggestion of an Organometallic Intermediate in an Intramolecular Dechlorination Reaction Involving Copper(I) and a ArCH₂Cl Moiety

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In a broad ongoing research program, we have studied a wide variety of (L)Cu^I/O$_2$ reactions aimed at the elucidation of copper−dioxygen adduct structure, spectroscopy, and reactivity, possibly also relevant to copper enzyme (bio)chemistry.[1,2] Such investigations include an emphasis on varying the nature of the ligand L, its denticity, donor atom identity, etc. While studying such reactions, we came upon[3,4] reductive dehalogenation reactions which also could be studied for their scope and mechanism of these transformations, such as

$$2 L Cu^I + 2\, R{-}Cl \rightarrow 2 L Cu^{II}{-}Cl + R{-}R \qquad (1)$$
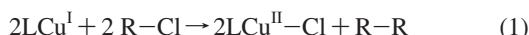
In fact, there are a good number of literature reports on copper-ion-mediated R−X dehalogenations;[5–7] a very active subfield includes atom transfer radical addition (ATRA) and polymerization (ATRP) employing copper(I) complexes with tri- or tetradentate N ligands.[8,9] A variety of copper (and iron) enzymes, those normally involved in the biological O$_2$ processing, are also able to reductively dehalogenate R−X substrates (with reduced Cu^I enzymes) or oxidize them via Cu^I/O$_2$ chemistry.[4,10] Investigations of such R−X/Cu−enzyme reactivity have been of interest with regards to detoxification and remediation of halogenated (particularly chlorinated) organic pollutants.[4,10,11]

As part of a recent mechanistic investigation,[3] we described the ability of (TMPA)Cu^I (TMPA ≡ TPA ≡ tris(2-pyridylmethyl)amine) to dehalogenate R−X substrates (e.g., CH$_2$Cl$_2$, allyl chloride, CHX$_3$, and PhCH$_2$X; X = Cl, Br, I) to form [(TMPA)^{R}Cu^{II}X]$^+$ and C−C coupling products (eq 1). With benzylic halides, kinetic analysis revealed second-order behavior in both reactants, rate = k[Cu]^2[R−X]^2. A reaction mechanism involving a copper(III)−halide intermediate was thus proposed, with supporting evidence coming from electronic effects observed with *p*-substituted substrates (Hammett plot), a rate dependence on the C−X bond dissociation energy, as well as ligand effects. In this report, we provide further insights from the study of a TMPA analogue possessing an internal ligand R−Cl substrate, a chloromethylene group in a pyridyl 6-position of one TMPA arm (Scheme 1). The results provide evidence for the formation of a rarely seen organometallic Cu−CH$_2$Ar species, forming in the initial reaction stages.

The ligand employed here, 6ClCH$_2$−TMPA (Scheme 1), was previously synthesized.[4] As the reaction under study began immediately following a combination of metal ion source and ligand, it was not possible to isolate a 6ClCH$_2$−TMPA−Cu^I complex. Thus, when anaerobic CH$_3$CN (or THF) solutions of
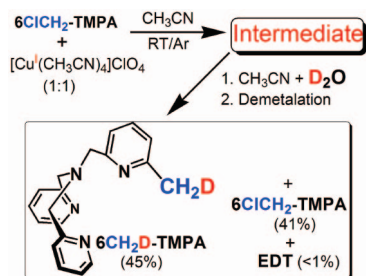
Scheme 1
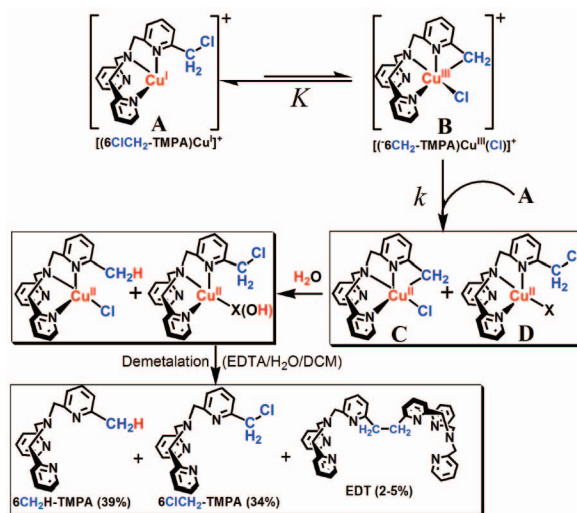
6ClCH$_2$−TMPA and [Cu^I(CH$_3$CN)$_4$]Y (Y = ClO$_4$ or B(C$_6$F$_5$)$_4$) are combined in a 1:1 stoichiometric ratio (concn ∼ 8.7 × 10^{-3} M) at room temperature, a color change from yellow (strong UV absorption) to green (formation of multiple d−d bands; λ_{max} = 710, 860, and 950 nm) occurs on a multihour time scale.[12] For product analyses, "synthetic scale" (∼0.3 mmol) reactions were allowed to stand overnight; workup consisted of addition of Na$_2$EDTA$_{(aq)}$ to chelate copper into an aqueous phase, while organics were extracted into CH$_2$Cl$_2$. Chromatographic separation and identification by ESI-MS and NMR spectroscopy[12] revealed a roughly 1:1 ratio (34–39% isolated yields) of the starting ligand 6ClCH$_2$−TMPA and a new methyl−TMPA product, 6CH$_2$H−TMPA; a tiny amount of C−C coupled product EDT was also isolated in 2–5% yields (Scheme 1).[12] The latter product undoubtedly comes from typical eq 1 chemistry; however, its very low yield indicates that the dominating chemistry is different, as proposed and outlined in Scheme 1. To start, the Cu^I ligand adduct [(6ClCH$_2$−TMPA)Cu^I]$^+$ (**A**) rapidly undergoes a reversible *intra*molecular oxidative insertion of the C−Cl substrate, giving intermediate **B**. A rate-determining electron transfer from a second molecule **A** ensues, giving **C** + **D**; the latter species maintains its chloromethylene group. Following this, protonation (by solvent–water) of the organometallic leads to a methyl−pyridyl containing product, as shown. Support for Scheme 1 is given below, in detail, including product analysis of both metal-containing and metal-free reaction mixture solutions, a kinetic

Scheme 2

study and information supporting the step involving protonation of an organometallic intermediate.

Further support for Scheme 1 comes from the ESI-MS identification of the inorganic products, those observed prior to workup which removes the copper(II) ion. We find parent ion peaks which correspond to the products $[(6ClCH_2-TMPA)Cu^{II}(Cl)]^+$ {$m/z = 438.07$} and $[(6CH_2H-TMPA)Cu^{II}(Cl)]^+$ ($m/z = 402.27$).[12] Confirmation comes from the direct comparison of ESI-MS data obtained from the same compounds which could be separately synthesized[13] and characterized (including X-ray).[12] Copper(I) complexes {$[(6ClCH_2-TMPA)Cu^I]^+$ {$m/z = 401.37$} and $[(6CH_2H-TMPA)Cu]^+$ {$m/z = 367.44$} are also observed, as a consequence of reduction of copper(II) to copper(I) in the ESI-MS experiment itself. In all cases, correct isotope patterns due to $^{63,65}Cu$ and/or $^{35,37}Cl$ are observed.[12]

The intramolecular reaction of 1:1 $Cu^I/6ClCH_2-TMPA$ (room temperature in THF) was followed by monitoring the increasing intensity of the product complexes d−d absorption bands (for Cu^{II}) (vide supra) with time.[12] The reaction follows a second-order dependence in the copper complex, with $k/M^{-1} s^{-1} = 2.9 \times 10^{-4}$ as determined by standard methods. This observation supports the Scheme 1 mechanism, where following the reversible insertion of copper(I) into the C−Cl bond leading to organo−copper(III) intermediate **B**, a conproportionation of **B** with the original ligand−Cu(I) complex **A** leads to intermediates **C** and **D** (thus, rate = $kK[Cu(I)]^2$). This would be followed by a rapid protonation of **C** leading to the observed products. The initial **A/B** equilibrium step probably lies far to the left, so that the concentration of organo−copper(III) speceis **B**, a proposed intermediate for the C–C coupling reaction leading to EDT (Scheme 1),[3] is always very low. This likely is the reason why the dimerization reaction giving EDT became a minor process in the present system.

We postulate that solvent–water serves as an acid to release the methyl−pyridyl product observed (Scheme 1). When 1 equiv of $[H(OEt_2)_2]^+[B(C_6F_5)_4]^-$ was added to the $6ClCH_2-TMPA$ /$[Cu^I(CH_3CN)_4]^+$ 1:1 reaction mixture, workup shows that the reaction profile remains essentially unchanged, with ca. 1:1 ratios (experimentally in 36–43% isolated yields) of $6ClCH_2-TMPA$ and $6CH_2H-TMPA$ obtained (plus 2% EDT). Similar ESI-MS data were again obtained for both prior and post EDTA treatments.[12]

Further support comes from the observation that addition of D_2O to the initial reaction mixture leads to $6CH_2D-TMPA$ {45%, isolated, $m/z = 306.46$ (M + H), 328.42 (M + Na)} and $6ClCH_2-TMPA$ (41%, isolated), again in a ~1:1 mixture; here, the yield of EDT was <1% (Scheme 2). Correspondingly, analysis prior to EDTA treatment reveals $[(6CH_2D-TMPA)Cu^{II}(Cl)]^+$ ($m/z = 403.24$) and $[(6CH_2D-TMPA)Cu^I]^+$ ($m/z = 368.45$), with correct isotope patterns. The ESI-MS data also indicate that a greater than 99% deuterium incorporation occurs. ^2H NMR spectroscopy of the isolated organic confirms the formation of only $6CH_2D-TMPA$ (δ, 2.6 ppm).[12] The combined results suggest that, as is common in organometallic chemistry,[14,15] deuteronation of a metal−alkyl, here a copper(II)−alkyl species (Scheme 1), releases the deuteronated organic, here the methyl−pyridyl fragment $6CH_2D-TMPA$.

Another compelling piece of evidence points to the presence of a copper organometallic species, that is, with a carbanionic $6-^-CH_2-TMPA$ moiety. When benzaldehyde is added to the initial reaction mixture, both copper complex and isolated organic products detected include the $6PhCH(OH)CH_2-TMPA$ moiety.[12] Thus a nucleophilic attack on PhC(O)H has occurred, this being a common behavior in organometallic chemistry.[14,16]

Recent experimental and theoretical research have provided insights into an elusive copper(III) intermediate in C−C coupling reactions by lithium organocopper chemistry.[17–19] Only a few formally Cu(III) compounds with Cu−C bonds are known.[17,20]

Thus, in contrast to reactions of copper(I) complexes with exogenous organohalide substrates, the present ligand design affords a reductive dechlorination reaction involving an "internal" chloromethylene substrate. The results provide clear chemical evidence for the involvement of a Cu−alkyl intermediate, $Cu^{III}-R$ and then $Cu^{II}-R$, as described by Scheme 1.

Supporting Information Available: Synthetic and reactivity details, product analyses/characterization, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See Supporting Information.
(13) $[\{(6ClCH_2-TMPA)Cu^{II}(Cl)\}_2]^{2+}$ and $[\{(6CH_2H-TMPA)Cu^{II}(Cl)\}_2]^{2+}$ were generated by reaction of $[Cu^I(CH_3CN)_4]Y$ (Y = ClO_4 or $B(C_6F_5)_4$) plus isolated $6ClCH_2-TMPA$ or $6CH_2H-TMPA$, in THF/CHCl_3 via solvent (chloroform) reductive dechlorination processes. See ref 4.
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