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LETTER

Oxidative dehalogenation during a copper complex mediated hydroxylation reaction

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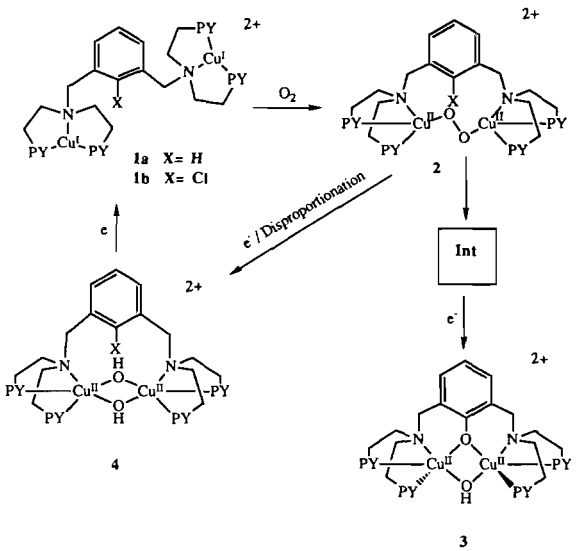

Scheme 1.

The presence of large quantities of halogen-substituted organics in the environment, along with the proven toxicity or carcinogenicity of these compounds, has led to increased activity in the study of chemical processes which result in their dehalogenation. For example, procedures or approaches being used to effect carbon–chlorine bond cleavage include reaction with superoxide ion [1], reductive coupling [2], photolytic reactions [3], the use of bacterial action [4] and the direct use of oxygenase enzymes [5]. While some of these methods utilize metal ion mediated reactions [3], the employment of transition metal catalyzed processes has been largely unexplored [6]. Here, we report a novel case of a metal ion induced oxidative dehalogenation, the first copper mediated hydroxylation induced dechlorination of an aromatic substrate. The reaction observed is reminiscent of the known action of iron (and perhaps copper; a bacterial copper-dependent phenylalanine hydroxylase is known [7]) phenylalanine hydroxylase (PAH), where a 4-chloro phenylalanine substrate produces both tyrosine (dechlorination) and 3-chlorotyrosine (migration) [5a]. Iron PAH is also known to defluorinate 4-fluoro phenylalanine [5b].

In a reaction which bears close analogies to those observed in copper monooxygenases, we have previously shown [8] that reaction of dicopper(I) complex **1a** with O_2 produces the phenoxo and hydroxo-bridged dicopper(II) complex **3** (Scheme 1). We have also established that a $\{Cu_2–O_2\}^{2+}$ intermediate (**2**) forms in the initial reaction with dioxygen [9]. The formation of at least one additional intermediate in the overall process where **1**→**3** (Scheme 1, **Int**) is likely, since when X = methyl, a migration reaction occurs [10, 11]; this is proposed to proceed through a carbonium ion intermediate formed by the electrophilic attack of the bound peroxo moiety in **2** upon the aromatic ring [12]. Here, we find that when the halogenated derivative **1b**** is reacted with O_2 at room temperature in CH_2Cl_2, no product resulting from migration occurs; instead, a 20% yield of hydroxylated and dechlorinated compound **3** is isolated. The only other product observed was the dihydroxo dicopper(II) complex **4b** resulting from oxidation of Cu(I) without hydroxylation of xylyl ligand [12]†.

Following the early observation that dehalogenation of 4-fluoro or 4-chloro phenylalanine is ac-

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Compound $[Cu^I_2(XYL–Cl)](PF_6)_2 \cdot CH_2Cl_2$ (1b**) was prepared by stirring a CH_2Cl_2 solution of the ligand XYL–Cl with two equivalents of $[Cu(CH_3CN)_4](PF_6)$ and precipitating with diethyl ether under an argon atmosphere. *Anal.* Calc. for $Cu_2C_{37}H_{41}Cl_3N_6P_2F_{12}$: C, 40.71; H, 3.79; N, 7.70. Found: C, 40.74; H, 3.75; N, 7.57%. ^1H NMR (300 MHz) (d_3-nitromethane; δ) 3.19 (s, br, 16H), 3.84 (s, br, 4H), 5.39 (s, 2H(CH_2Cl_2)), 6.96–7.70 (m, br, 15H), 8.48 (d, br, 4H(py-6)).

†Compound **4b** precipitated from CH_2Cl_2 solution. It was recrystallized from acetone/Et_2O and isolated as a solvate with formula $[Cu^{II}_2(XYL–Cl)(OH)_2](PF_6)_2 \cdot 2H_2O \cdot 0.25(CH_3)_2CO$. *Anal.* Calc. for $Cu_2C_{36.75}H_{46.50}ClN_6O_{4.25}P_2F_{12}$: C, 40.40; H, 4.26; N, 7.69. Found: C, 40.41; H, 3.73; N, 7.69%. IR (Nujol; cm^{-1}): 3610(w, br, OH), 3605(w, br, OH), *c.* 3400(br, H_2O), 1705(m, $CH_3C(O)CH_3$), 840(PF_6). UV–Vis (CH_3CN) λ_{max} (ϵ, M^{-1} cm^{-1}) 262(23 000), 295(sh, 7180), 704(210). Molar conductivity (DMF): $\Lambda_M = 130.0$ Ω^{-1} cm^2 mol^{-1}.

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TABLE 1. Copper mediated hydroxylation induced oxidative dehalogenation[a]

No.	Substrate	Reductant	Solvent	Yield (%)[b]
1	$[Cu_2^I(XYL–Cl)]^{2+}$	X	CH_2Cl_2	20
2	$[Cu_2^I(XYL–Cl)]^{2+}$	$CrCl_2$	CH_2Cl_2	37
3	$[Cu_2^I(XYL–Cl)]^{2+}$	$CrCl_2$	CH_3OH	<10
4	$[Cu_2^I(XYL–Cl)]^{2+}$	Zn	CH_3CN	50
5	$[Cu_2^I(XYL–Cl)]^{2+}$	Zn	CH_2Cl_2	75
6	$[Cu_2^I(XYL–Cl)]^{2+}$	sodium ascorbate	CH_3CN	40
7	$[Cu_2^I(XYL–Cl)]^{2+}$	sodium ascorbate	CH_2Cl_2	52
8	$[Cu_2^I(XYL–Cl)]^{2+}$	1,2-diphenylhydrazine	CH_2Cl_2	42
9	$[Cu_2^I(XYL–Cl)]^{2+}$	Zn (under Ar)[c]	CH_2Cl_2	no dehalogenation
10	XYL–Cl	Zn	CH_2Cl_2/H_2O	no dehalogenation
11	XYL–Cl + $Cu^{II}(NO_3)_2$	Zn	CH_2Cl_2/CH_3OH	75

[a]Typically an excess of reductant and the substrate were stirred under argon in a particular solvent and then oxygenated for 24 h at room temperature. [b]Isolated yield. [c]This reaction was carried out in the absence of dioxygen.

companied by the reaction of more than the usual stoichiometric amount of NADH reductant [5a, b], we also examined the reaction of dicopper(I) complex **1b** with O_2 in the presence of various chemical reductants. The results are given in Table 1. In a typical reaction, **1b** and a slight excess of appropriate reductant were stirred in a given solvent and after one-half hour, the mixture was exposed to an atmosphere of dry dioxygen for 24 h. The product **3** was isolated by filtration and crystallization from CH_2Cl_2/Et_2O.

From the experiments outlined in Table 1, the following conclusions can be drawn.

1. A heterogeneous mixture of the dicopper(I) complex **1b**, O_2 and Zn dust (as reductant) in CH_2Cl_2 gives the best overall yield (~75%) of oxidatively dechlorinated product **3**. Diphenylhydrazine and sodium ascorbate provide consistently lower product yields, even when the latter is run under mixed phase conditions and with a phase transfer catalyst. Chromous chloride also works but is not efficient.

2. Methanol is not a good solvent for this reaction, possibly due to the low solubility of both copper(I) and copper(II) complexes in this medium.

3. Experiments 9–11 indicate that both a copper(I) complex of the chlorinated ligand (e.g. **1b**), and dioxygen are required for the dehalogenation to occur. If the complex of the ligand is in the Cu(II) oxidation state, prior reduction to Cu(I) and subsequent reaction with O_2 are necessary.

Along with the prior evidence collected concerning the course of reaction of **1a** to give **3** [8], we can suggest an overall scheme relating what is already known to the course of action observed for the dehalogenation of **1b** in the presence of a reductant such as Zn. The peroxo dicopper(II) complex **2** forms when **1** is reacted with O_2, as has also been established when X=F [13]. Attack upon the arene substrate to give an intermediate (**Int**) can lead to hydroxylation, but this is inefficient when X=Cl*, unless a reductant is present; if the latter is true, **Int** can be reduced, the chlorine substituent can 'leave' as Cl^- and be captured as $ZnCl_2$. The inefficiency of this process also results in the conversion of **2** to **4**, either by disproportionation, or by reduction of **2** (possibly by **1b**). Since zinc can also reduce **4** to **1** (as has been established independently), the cycle gets repeated until either chlorinated ligand complex **1b** or the Zn are depleted and good yields of **3** are produced. Zinc metal can also reduce **3** to a dicopper(I) complex, but this is known to reoxidize to the same material [14].

A fuller understanding of the mechanism awaits additional studies involving X-substituted *m*-xylyl complexes. We note that under similar conditions, the fluoro-substituted analogue of **1** (X=F) gives only a trace of oxidatively dehalogenated product **3**, even in the presence of extra reductants [15]*. The present study indicates that oxidatively induced dehalogenation reactions can be effected by copper ion, and the present system may serve as an interesting model for the action of metal-containing oxygenases upon chlorinated substrates. Such studies may also suggest strategies for new chemical approaches to the detoxification of chlorinated organics.

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*This may be due to the slower ring electrophilic attack resulting from the electron-withdrawing halogen substituent. Preliminary kinetic studies on 5-X-substituted (rather than 2-substituted) *m*-xylyl analogues of **1** are consistent with this hypothesis.

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