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Cu(II)-CATALYSIS IN THE REDUCTION OF N,O-DIBENZOYLHYDROXYLAMINE BY A TERTIARY AMINE

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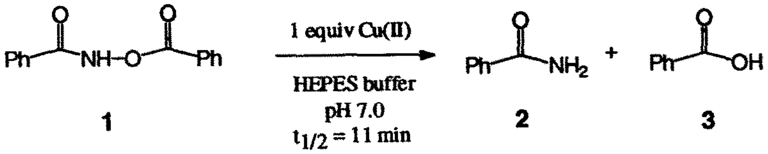
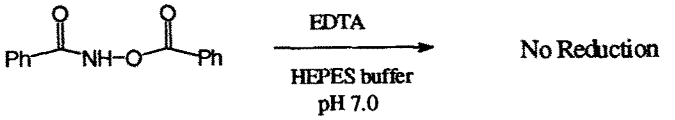
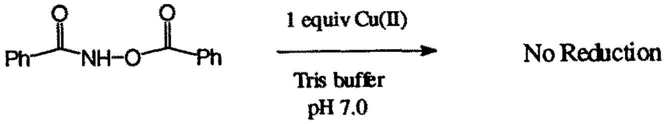
Summary: Cu(II) catalyzes the reduction of N,O-dibenzoylhydroxylamine by HEPES buffer to yield benzamide and benzoic acid.

The reductive cleavage of hydroxylamine and its derivatives is affected with a wide assortment of reducing agents.[1] Novak has described the reduction of N-aryl-O-pivaloyl hydroxylamines with reducing metals such as Fe(II) and Cu(I).[2] We have subsequently observed that Cu(I), but not Cu(II), likewise reduces O-benzoylhydroxylamine (i.e., benzoisohydroxamic acid) to benzoic acid and ammonia.[3] In the course of our work on potential Cu(II)-catalyzed hydrolytic reactions of hydroxylamine derivatives, we have found that Cu(II) catalyzes the reductive cleavage of N,O-dibenzoylhydroxylamine in aqueous buffered solution. To the best of our knowledge, this is the first observation of reductive bond cleavage catalyzed by the aquo-Cu(II) ion.

An 0.1 mM solution of N,O-dibenzoylhydroxylamine (1)[4] in 0.2 M HEPES buffer (adjusted to pH 7.0 with KOH) is stable over the course of several days. Upon addition of one equivalent of $Cu(ClO_4)_2$ at ambient temperature, HPLC indicates the simultaneous formation of benzamide (2) and benzoic acid (3) with a half-life of about 11 minutes. Confirmation of the







benzamide product was obtained by scaling the reaction to 250 mg and isolating the benzamide (identical to an authentic sample using ^1H and ^{13}C NMR) in 84% isolated yield. The reaction rate increases with [Cu(II)] from 0.02-0.5 mM.[5] With 0.2 and 0.5 equivalents of Cu(II) the reactions proceeded to completion, indicating turnover behavior. In the presence of EDTA, no reduction is observed under the same conditions.

Our observation of complete reaction even when only 0.2 equivalents of Cu(II) are present requires an external reductant. We have concluded that the HEPES [N-(2-hydroxyethyl)piperazine-N'-2-ethanesulfonic acid] buffer serves as the ultimate reducing agent, and that Cu(II) serves as a catalyst for the redox reaction. The same reaction of 1 with Cu(II) (up to 100 equivalents) carried out in Tris [tris(hydroxymethyl)methylamine] buffer at pH 7.0 does not give reduction products, but instead yields slow hydrolysis at the same rate as without added Cu(II). Because HEPES is a 3° amine buffer, its oxidation potential is lower than that of Tris, a 1° amine buffer. This experiment was based on the findings of Sayre, who has reported that the batho-Cu(II) complex is reduced by HEPES but not by Tris.[6] While it is possible that Tris serves instead to effectively remove Cu(II) from reaction by complexation, this could not explain how complete reduction is observed with subequivalent amounts of the metal ion.

We envision three potential roles for copper: (a) 1 oxidizes Cu(II) to Cu(III), which is subsequently re-reduced to Cu(II) by HEPES; (b) HEPES reduces Cu(II) to Cu(I), which is subsequently re-oxidized to Cu(II) by 1; or, (c) HEPES reduces only the Cu(II)-1 complex. Mechanism (a) seems unlikely, given that the Cu(III) oxidation state appears to be inaccessible in water except when stabilized by polyanionic chelating ligands.[7] Furthermore, if this mechanism were operative we should have seen reduction by Cu(II) even when using Tris buffer. Mechanisms (b) and (c) cannot be distinguished as easily. While Novak's work points to Cu(I)'s reactivity towards O-acylhydroxylamines, Sayre's work indicates that batho-Cu(II) is reduced by HEPES but aquo-Cu(II) is not. Either mechanism (b) is operating in which aquo-Cu(I) is formed under steady-state conditions, or the reaction proceeds via mechanism (c).

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