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Cu(II)-PROMOTED HYDROLYSIS OF *N*-BENZOYLIMINODIACETIC ACID

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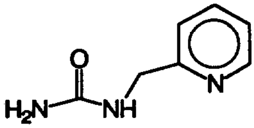
Summary: *N*-Benzoyliminodiacetic acid experiences Cu(II)-promoted amide hydrolysis interpretable as resulting either from amide *N*-coordination or *O*-coordination with intramolecular carboxylate catlysis.

Metal ions and their complexes are known to promote or catalyze the hydrolyses of amides, a biologically-relevent reaction that is otherwise very slow.[1] The mechanisms cited most often to rationalize accelerated hydrolysis are Lewis acid (coordination to the carbonyl oxygen), metal hydroxide (attack of metal-bound hydroxide on the carbonyl carbon), or both simultaneously.[2] Less often suggested is direct coordination of the amide nitrogen to the metal, which would be expected to yield a complex with acyl transfer reactivity similar to that of an acid chloride if the amide is not deprotonated.[3] Of course, the oxygen of a neutral amide is a much stronger donor atom than is nitrogen as predicted by its greater basicity.[4] However, the protonation of a distorted amide occurs on nitrogen with resulting specific acid-catalysis of hydrolysis.[5] Maslak has reported that urea 1, which experiences rapid Ni(II)-promoted ethanolysis,[6] exists in the crystal as the *N*- rather than as the *O*-chelate.[7] Amide 2 likewise demonstrates Cu(II)-promoted methanolysis.[8] Because complexation is typically less favorable in water than in alcohol, and because copper cannot form deactivating μ-oxo dimers in alcohol solvents, we have asked whether or not hydrolysis



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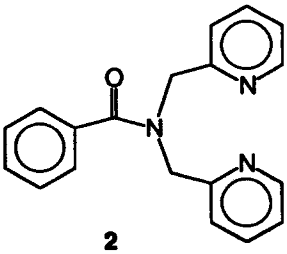

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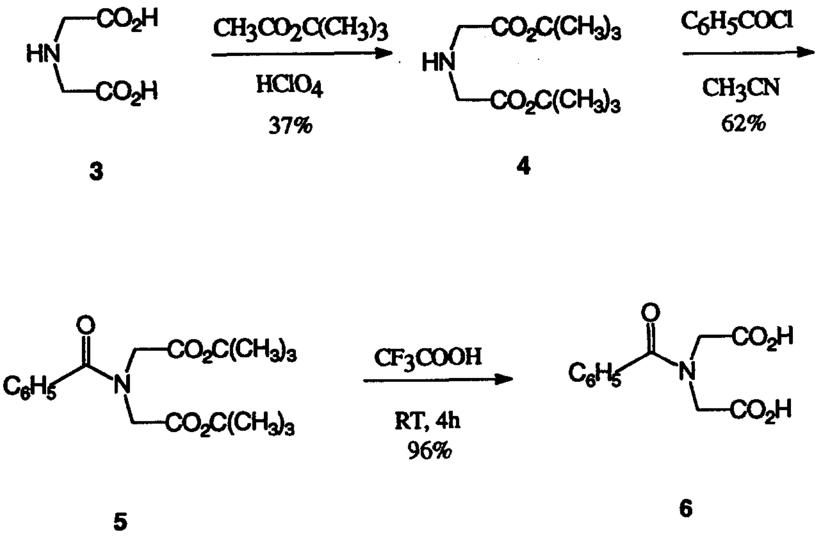
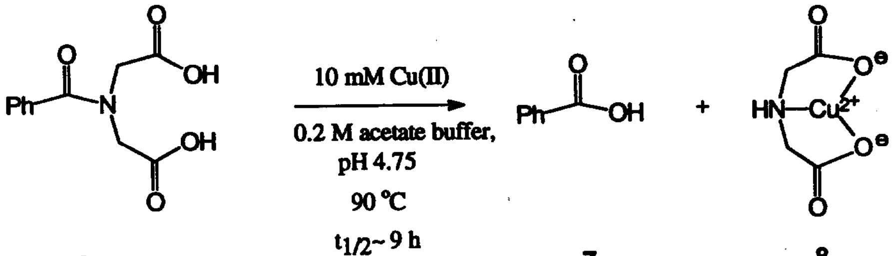
in water can be accelerated using the N-coordination mechanism. We now report that Cu(II) promotes the hydrolysis of water-soluble, chelating amide 3.

N-Benzoyliminodiacetic acid (6) was prepared by the benzoylation of the bis-t-butyl ester of iminodiacetic acid (4), followed by acid-catalyzed deprotection of the carboxylic acid

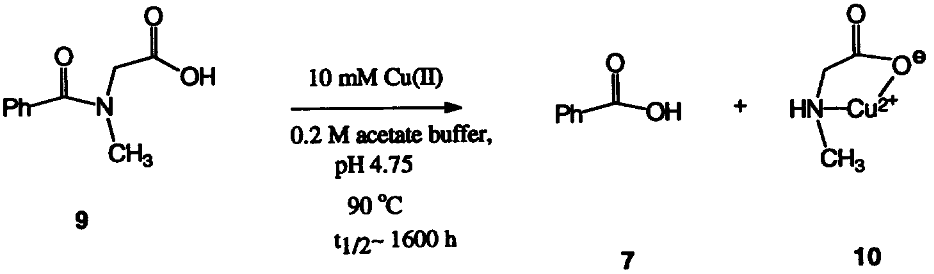


groups. Compounds 4, 5, and 6 demonstrated ^1H NMR, ^{13}C NMR, mass spectral, and microanalytical (6 as the monohydrate) properties supportive of the structure assignments. Amide 6 incorporates several useful properties: (1) the compound is water soluble; (2) it can form a tridentate complex only via amide N-coordination; and, (3) because it is a tertiary amide, complexes of 3 cannot deprotonate.[9]

Cu(II) acceleration of the hydrolysis reaction was observed at pH's greater than 3; however because of precipitation at pH's greater than 5, reactions were conducted using 6 (0.1 mM) in aqueous 0.2 M acetate buffer (pH 4.75) at 90°C, and the formation of benzoic acid was monitored using HPLC.[10] Without added metal, benzoic acid formation occurs with a $t_{1/2}$ of about 1500 h (an estimate is required because of the very long reaction time). The addition of $Cu(ClO_4)_2$ yields homogeneous reactions in which the formation of benzoic acid is accelerated; $Zn(ClO_4)_2$ and $Gd(ClO_4)_2$ likewise show rate accelerations, but much smaller than Cu(II). As shown in Table 1, the reaction rates increase with Cu(II) concentration up to and including 1000-equivalents, consistent with weak complexation.



6 **7** **8**



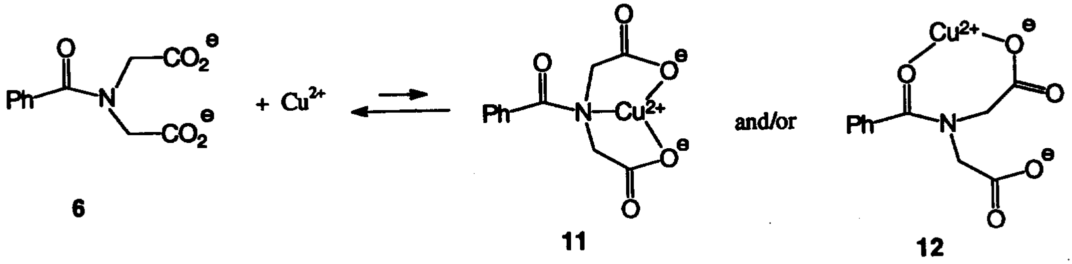
9 **7** **10**

Table 1. Effect of Cu(II) concentration on the rate of benzoic acid formation from 6 (0.1 mM) in aqueous 0.2 M acetate buffer (pH 4.75) at 90°C.

$[Cu(ClO_4)_2]$ (mM)	k_{obs} (min^{-1})	$t_{1/2}$ (h)
0 (EDTA)	ca. 8×10^{-6}	ca. 1500
1	5.0×10^{-5}	230
10	1.3×10^{-3}	8.9
100	7.9×10^{-2}	0.15

Notes- The pH of each reaction was adjusted prior to heating. Because of the inability to buffer at the highest Cu(II) concentration, this rate is less reliable than those at the lower concentrations.

Cu(II)-acceleration of 6's hydrolysis might result either from tridentate *N*-coordination (11; fused 5-membered chelate) or bidentate *O*-coordination (12; 7-membered chelate). In an effort to make this differentiation, the hydrolysis of compound 9 was examined. Under conditions that effect the hydrolysis of 6 with $t_{1/2}$~9 h (10 mM Cu(II)), the hydrolysis of 9 occurs with $t_{1/2}$ of about 1600 h. This result would be consistent either with an *N*-coordination mechanism or with an *O*-coordination mechanism with catalysis by the second carboxylate group of 6. It is not possible at present to distinguish between mechanistic possibilities 11 and 12; however, the fact that the reaction of 9 was carried out in 0.2 M HOAc/NaOAc buffer and is nonetheless slow argues against the kinetic significance of 12.



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10) HPLC was carried out on an IBM LC/9533 system using an IBM C-18 reversed phase column and a 20 μL injection loop. Elution was carried out at a flow rate of 1 mL/min using 0.2 M phosphate buffer (pH 2)/methanol (4:7) with UV detection of the eluant at 254 nm.

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