Chemoselective Hydrolysis of Amides in the Presence of Esters by Copper(II)/Glyoxal: Metal Complexation as the Core Motif for Selective Amide Activation

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Summary: A general method for selective hydrolysis of amides in the presence of esters with Cu(II)/glyoxal in aqueous medium is reported.

The hydrolyses of carboxamides and carboxylic esters are classical reactions of fundamental importance in chemistry and biology. Due to the large difference in the reactivities, the more reactive ester group can be selectively hydrolyzed in the presence of the less reactive amide group under controlled alkaline[1] or acidic[2] conditions or by enzyme reagents.[3] However, the "opposite selectivity", that is, the single-step hydrolysis of the amides to carboxylic acids without disturbing the esters, has not been realized under mild conditions despite long-standing concern.[4] Even most of the proteases hydrolyze the esters much faster than the corresponding amides.[5] In fact, the selective modification of a less reactive group in the presence of a similar but more reactive group, superseding the traditional, synthetically equivalent three-step protection–deprotection methodology, is one of the most cherished but challenging goals in organic synthesis.[6] Most of the few reported reactions of this kind involve the opposite selectivity between aldehyde and/or keto groups and are invariably based on some ingenious way of *in situ* protection of the more reactive carbonyl group.[6a,b] We wish to report a different approach that involves selective activation of the less reactive amide group for its selective hydrolysis in the presence of the ester group.

There is intensive interest in metal-ion-catalyzed/promoted hydrolysis of esters, amides and other functional groups due to its biochemical implications.[7] It appears that, in order to be catalytically active, the metal ion must be chelated prior to[7a] or during[7b,c] the reaction by using some suitable ligand or ligating sites suitably located in the substrate respectively, often involving the group to be hydrolyzed in the chelate ring. Thus, simple monodentate esters or amides are not hydrolyzed by nonchelated metal ions. However, when the hydrolysis occurs, the esters are still hydrolyzed faster than the amides.[7ac,8] The requirement of chelation for efficient metal-ion-catalysis has now been exploited by us in designing a protocol for selective activation of primary and secondary amides followed by hydrolysis. It involves *in situ* introduction of the additional ligating group at the nitrogen of the amide by using the reactivity of the N–H bond, a structural feature not present in the esters, toward aldehydes to give methylol-type derivatives.[9] We chose glyoxal for this purpose and embarked upon the possibility of its reaction with the amide at one of the aldehyde groups followed by chelation of Cu(II) ion through the other aldehyde group (or its hydrated form[10]) and the nitrogen of the amide group. Although the dichotomy of O vs N coordination in amides has been considered to be settled in favor of the more basic carbonyl oxygen,[11] emerging evidence[12] led us to feel that the nitrogen might be coaxed to form the chelate if it was better positioned than the carbonyl oxygen to do so. This would activate the amide carbonyl as well as the leaving group. This doubly-activated amide is expected to rival acid chlorides in electrophilic reactivity.[12] We were gratified to observe this probable behavior when a mixture of the amide and copper(II) chloride in aqueous 30% glyoxal was heated under gentle reflux at pH 3.5, affording the carboxylic acids in high yields[13] (Scheme 1). The results are shown in the Table 1.

Although the method is applicable to primary as well as secondary amides, our attention was focused on the

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(1) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis;* Wiley: New York, 1989; pp 252, 318, 330. Kaestle, K. L.; Anwer, M. K.; Audhya, T. K.; Goldstein, G. *Tetrahedron Lett.* **1990**, *32*, 327. Uskoković, M.; Rees, C.; Lee, H. L.; Grethe, G.; Gutzwiller, J. *J. Am. Chem. Soc.* **1971**, *93*, 5902.

(2) Landini, D.; Rolla, F. *J. Org. Chem.* **1982**, *47*, 154.

(3) Reviews: Ohno, M.; Otsuka, M. *Org. React.* **1989**, *37*, 1. Csuk, R.; Glaenzer, B. I. *Chem. Rev.* **1991**, *91*, 49. Boland, W.; Frössl, C.; Lorenz, M. *Synthesis* **1991**, 1049. In addition, there are numerous nonhydrolytic methods involving nucleophilic O-alkyl cleavage which is not possible in amides. Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron* **1993**, *49*, 3691. See also: Filippo, J. S., Jr.; Romano, L. J.; Chern, C.-I.; Valentine, J. S. *J. Org. Chem.* **1976**, *41*, 586 for cleavage with superoxide.

(4) Primary and secondary amides could be hydrolyzed selectively in the presence of an ester group with tetrachloro- or tetrafluorophthalic anhydride under rather drastic conditions (molten state, 135–170 °C, 2.5-6 days). Eaton, J. T.; Rounds, W. D.; Urbanowicz, J. H.; Gribble, G. W. *Tetrahedron Lett.* **1988**, *29*, 6553. Primary amides have been selectivley cleaved by nonhydrolytic methods involving nitrosative deamination. Woodward, R. B. *Pure Appl. Chem.* **1973**, *33*, 145. Oppliger, M.; Schwyzer, R. *Helv. Chim. Acta* **1977**, *60*, 43. Wolfrom, M. L.; Wood, H. B. *J. Am. Chem. Soc.* **1951**, *73*, 730. A few special types of secondary amides are also cleaved by nitrosation. Kim, Y. H.; Kim, K.; Park, Y. J. *Tetrahedron Lett.* **1990**, *31*, 3893. Patrick, T. B.; Dolan, J. G. *J. Org. Chem.* **1973**, *38*, 2828. Olah, G. A.; Olah, J. A. *J. Org. Chem.* **1965**, *30*, 2386. However, it is not generally applicable to secondary amides, although the nitrosoamide intermediate is more prone to nucleophilic attack than the amide (Garcia, J.; Vilarrasa, J. *Tetrahedron Lett.* **1982**, *23*, 1127. Saavedra, J. E. *J. Org. Chem.* **1979**, *44*, 860), it either still requires alkaline hydrolysis in an additional step to give the acid which may be incompatible with the esters (Rull, M.; Serratosa, J.; Vilarrasa, J. *Tetrahedron Lett.* **1977**, 4549. Kuehne, M. E. *J. Am. Chem. Soc.* **1961**, *83*, 1492) or undergoes thermal decomposition via a diazo ester to give a mixture of ester, acid, and alkene the composition of which depends on the structure of the amide and the solvent (White, E. H. *J. Am. Chem. Soc.* **1955**, *77*, 6011).

(5) Bender, M. L.; Kézdy, F. J. *Ann. Rev. Biochem.* **1965**, *34*, 49. Florkin, M.; Stotz. E. H. Eds. *Comprehensive Biochemistry*, 3rd ed.; Elsevier: London, 1973, Vol. 13, Chapter 2, p 6. Leanna, M. R.; Morton, H. E. *Tetrahedron Lett.* **1993**, *34*, 4485.

(6) (a) Maruoka, K.; Saito, S.; Concepcion, A. B.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1183. (b) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848. (c) Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970. (d) Doyle, M. P.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 4806.

(7) (a) Chin, J. *Acc. Chem. Res.* **1991**, *24*, 145. (b) Suh, J. *Ibid.* **1992**, *25*, 273. (c) Fife, T. H. *Adv. Phys. Org. Chem.* **1975**, *11*, 1. (d) Ram, R. N.; Varsha, K. *Tetrahedron Lett.* **1991**, *32*, 5829. (e) Zhu, L.; Kostic, N. M. *J. Am. Chem. Soc.* **1993**, *115*, 4566 and references cited therein.

(8) For leading references see: Przystas, T. J.; Fife, T. H. *J. Chem. Soc., Perkin Trans. 2* **1990**, 393. Also compare the following references: Duerr, B. F.; Czarnik, A.W. *J. Chem. Soc., Chem. Commun.* **1990**, 1707; *Tetrahedron Lett.* **1989**, *30*, 6951. Recently, however, some specially designed amides have been found to undergo metal-ion-catalyzed hydrolysis at a comparable or slightly faster rate than the corresponding esters. Suh, J.; Park, T. H.; Hwang, B. K. *J. Am. Chem. Soc.* **1992**, *114*, 5141.

(9) Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52.

(10) Glyoxal is known to exist as its monohydrate in equilibrium with other species in aqueous solution. Bedford, C. T.; Fallah, A.; Mentzer, E.; Williamson, F. A. *J. Chem. Soc., Chem. Commun.* **1992**, 1035.

(11) Sigel, H.; Martin, R. B. *Chem. Rev.* **1982**, *82*, 385.

(12) Chen, K.; Steven, P. W.; Czarnik, A. W. *Tetrahedron Lett.* **1992**, *42*, 6303.

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Scheme 1

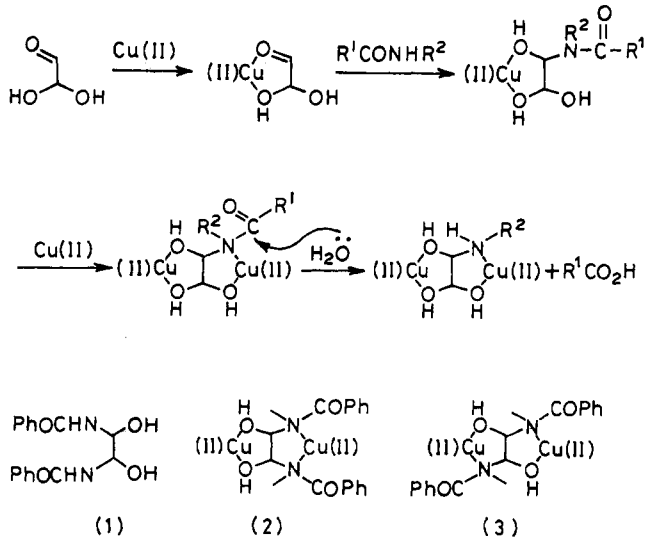

Table 1. Reaction of Amides and Esters with Copper(II) Chloride/Glyoxal

entry	substrate	reflux time (h)	isolated yield (%)
	amide		acid
1	$PhCONH_2$	8	80
2	PhCONHMe	11	82
3	*p*-MePhCONHMe	15	77
4	*p*-OMePhCONHMe	24	86
5	*p*-NO_2PhCONHMe	24	50
6	PhCH=CHCONHMe	12	92
7	PhCONHEt	24	70
8	$PhCONMe_2$	15	88[a]
9	$Me(CH_2)_{16}CONHMe$	24	93
	ester		recovered ester
10	$PhCO_2Me$	11	80
11	*p*-$MePhCO_2Me$	15	85
12	*p*-NO_2PhCO_2Me	24	84
13	$PhCH{=}CHCO_2Me$	12	99
14	$PhCO_2Et$	24	78
15	$Me(CH_2)_{16}CO_2Me$	24	95
	amide + ester		
16	PhCONHMe + *p*-NO_2PhCO_2Me	24	$PhCO_2H$ (80) + *p*-NO_2-$PhCO_2Me$ (99)
17	$Me(CH_2)_{16}CONHMe$ + $Me(CH_2)_{16}CO_2Me$	32	$Me(CH_2)_{16}CO_2H$ (90) + $Me(CH_2)_{16}CO_2Me$ (98)

[a] Recovered starting amide.

hydrolysis of secondary amides, which is of considerable synthetic and degradative value but, nevertheless, the most problematic[14] of the three classes of amides. The method works well with *N*-methyl- and *N*-ethylbenzamide, but other N-monosubstituted (n-Pr, i-Pr, n-Bu, Ph, benzyl, cyclohexyl) benzamides were quantitatively recovered unchanged probably due to the steric effect. Thus, selective hydrolysis of *N*-methyl- and *N*-ethylamides can be done in the presence of other secondary amides. As expected, the esters, either alone or in competition with the amides (Table 1, entries 16 and 17), and tertiary amides (*N*,*N*-dimethylbenzamide) are mostly recovered unchanged. However, activated esters, such as *p*-nitrophenyl and *p*-carboxyphenyl acetates, do not survive. The C–H bonds α to a keto group appear to remain unaffected under the experimental conditions. That the reaction is hydrolytic was revealed by the usual tests for amines responded to by the reaction medium on basification, following the isolation of the acid.

Taking *N*-methylbenzamide as the test case, it was shown that proton-catalyzed hydrolysis is insignificant under the reaction conditions as ≥90% recovery of the unchanged amide was observed on reaction in dilute HCl even at higher acid concentrations (up to pH 2). Further, no reaction occurred in the absence of either of the reagents. Thus, Cu(II) appears to also catalyze the otherwise not generally successful condensation of secondary amides with glyoxal in contrast to that with formaldehyde.[15] The catalysis of the condensation step may be explained by chelation of Cu(II) with glyoxal which in turn is indicated by the blue shifts of UV absorption maxima of glyoxal and copper(II) chloride from 275 to 250 nm and from 830 to 815 nm, respectively, observed on mixing the two reagents in an equimolar ratio. It appears that the reactants and the amine product are only loosely bound to the metal, as the hydrolysis occurs even with a catalytic amount (20 mol %) of Cu(II), though longer reaction time (28 h for *N*-methylbenzamide) is required for the complete hydrolysis.

That both the reaction of the amide with glyoxal and chelation are important for the reaction is shown by the failure of 30% aqueous solutions of oxalic acid, glycolic acid, ethylene glycol, and formalin to be used in place of glyoxal under similar conditions, whereas 30% aqueous glyoxylic acid can successfully replace glyoxal at the natural pH of the mixture. However, at this lower pH, the esters do not survive. When the pH was raised to the usual value of 3.5, the hydrolysis did not proceed, presumably due to deactivation of the aldehyde group because of ionization of the carboxyl group of glyoxylic acid. The bis-adduct **1**, prepared separately by the reaction of benzamide with glyoxal,[15a] does not undergo hydrolysis under similar conditions probably due to very weak chelation of Cu(II) involving the two amide nitrogens in the same (**2**) or both (**3**) the rings.[16]

The protection of the carboxylic acids as amides has seldom been used in synthesis in contrast to esters,[17] despite the fact that amides are more resistant to hydrolytic and nucleophilic conditions and have operationally more convenient physical properties than the esters. The underutilization of the amides in this respect is primarily due to the nonavailability of mild and selective methods for the deprotection step. The present methodology may develop into a selective method for the deprotection of acids from their *N*-methyl- and *N*-ethylamides.

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(13) **General Procedure**: A mixture of the amide (5 mmol) and copper(II) chloride (5.5 mmol) in aqueous 30% glyoxal (12 mL) was taken, and the pH was adjusted to 3.5 by adding 10% NaOH (~1.6 mL). Above this pH, precipitation of copper species occurs. The mixture was heated at gentle reflux. The progress of the reaction was monitored by TLC. Water-soluble carboxylic acids were isolated by filtration of the blue insoluble solid (a complex of copper(II) with glycollic acid) and extraction of the filtrate with ether. The water-insoluble acids were separated from the insoluble copper complex by treatment with organic solvents. The addition of NaOH to the reaction mixture is not necessary for the reaction; however, without the addition of NaOH, the esters are partially hydrolyzed. The competition experiments were performed by heating at reflux a mixture of amide (5 mmol), ester (5 mmol), $CuCl_2 \cdot 2H_2O$ (5.5 mmol), and glyoxal (12 mL) at pH 3.5.

(14) Tsunoda, T.; Sasaki, O.; Takeuchi, O.; Ito, S. *Tetrahedron* **1991**, *47*, 3925.

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(16) It appears that formation of two chelate rings of some degree of stability is necessary for the reaction to occur, ref 12.

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