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Communications

Metal Ion Catalysis of Amide Hydrolysis. Very Large Rate Enhancements by Copper(II) in the Hydrolysis of Simple Ligand-Functionalized Tertiary Amides[1]

Metal ion catalysis of hydrolytic processes is an area of continued intense investigation. *Ester* hydrolysis was early recognized[2] to be subject to catalytic rate accelerations as high as 10^8. Also, for the hydrolysis of glycin*amide*, both electrophilic (carbonyl) activation and intramolecular metal hydroxide mechanisms were shown to be associated with rate enhancement factors (REFs) of ca. 10^6 for *exchange-inert* Co(III).[3,4] However, *exchange-labile* metal ions appeared to exert relatively small catalytic effects in the hydrolysis of simple coordinating aliphatic amides[5] such as glycylglycine.[6,7] Thus, the reports by Groves and co-workers that the hydrolysis of specially designed aliphatic lactams is subject to REFs as large as 10^7 for Cu(II) and Zn(II)[8] appeared to suggest that the earlier amide systems lacked certain crucial structural features required for the observation of large catalytic effects.

Upon reexamination of the "old" studies, we concluded[9] that quite large REFs were actually in force, but were being masked by metal ion-coordination-induced amide NH deprotonation. For example, for glycylglycine the pH rate profile of Cu(II)-catalyzed hydrolysis is bell-shaped, reaching a maximum REF of ~100 at pH 4.2–4.4,[6a,b] the titration midpoint for generating a hydrolytically inert[6b,10] tridendate Cu(II) complex containing deprotonated amide.[11] On the basis of the unit-slope portion of the ascending leg of the pH rate profile (Cu^{II} catalysis of HO^--dependent hydrolysis), we predicted[9] that a REF of $\sim 2 \times 10^7$ would be observable at pH 7 if amide NH deprotonation were prevented. *In this communication, we show that REFs of this magnitude can be realized for aliphatic amide hydrolysis simply by use of tertiary (N-methyl) rather than secondary amides.*

The most obvious strategy would be to compare glycylsarcosine to glycylglycine. However, in order to avoid the additional complication that such dipeptides undergo diketopiperazine formation in competition with hydrolysis,[7] we settled on the comparison between picolinylsarcosine (Pic-Sar, **1**) and picolinylglycine

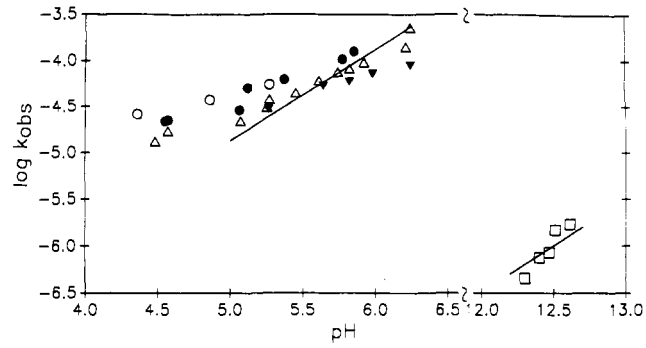

Figure 1. Plot of log k_{obs} vs pH for the hydrolysis of Pic-Sar (2 mM) in the absence (□) and presence of 1 mM (▼), 2 mM (△), 4 mM (●), and 10 mM (○) $Cu(NO_3)_2$ in water–ethylene glycol (2:1) at 50 °C with μ = 0.1 M. The lines drawn represent unit slopes for the uncatalyzed and 1-equiv Cu(II)-catalyzed cases.

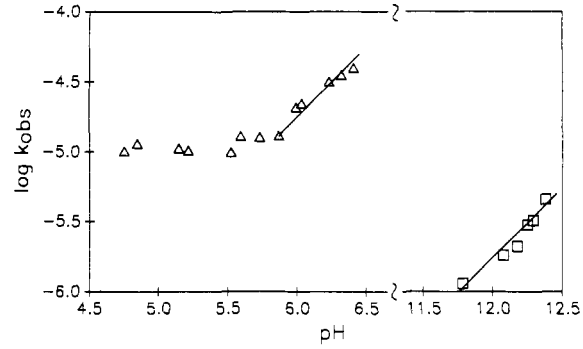

Figure 2. Plot of log k_{obs} vs pH for the hydrolysis of (6-COOH)Pic-Sar (2 mM) in the absence (□) and presence of 2 mM $Cu(NO_3)_2$ (△) in water–ethylene glycol (2:1) at 50 °C with μ = 0.1 M. The lines drawn represent unit slopes for the uncatalyzed and 1-equiv Cu(II)-catalyzed cases.

(1) Preliminary accounts of this work have been presented: Jacobson, A. R.; Sayre, L. M. *Abstracts of Papers*, 191st National Meeting of the American Chemical Society, New York, April 14–18, 1986; American Chemical Society: Washington, DC, 1986; INOR 233. Tang, W.; Reddy, K. V.; Sayre, L. M. *Abstracts of Papers*, 200th National Meeting of the American Chemical Society, Washington, DC, Aug 26–30, 1990; American Chemical Society: Washington, DC, 1990; INOR 225.
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(3) For a review, see: Sutton, P. A.; Buckingham, D. A. *Acc. Chem. Res.* **1987**, *20*, 357.
(4) The Co(III) systems should be regarded as examples of metal ion *promotion* rather than metal ion *catalysis*, since Co(III) is stoichiometrically coordinated to the product glycinate (there is no turnover). It is difficult to assess to what extent this thermodynamic preference skews the observed rate enhancements.
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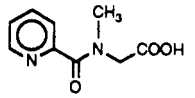
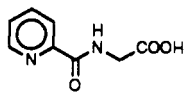
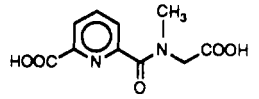
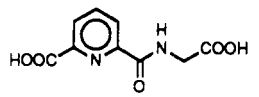
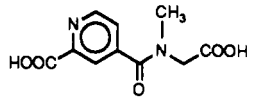
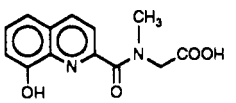
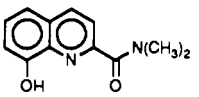
Table I. Spontaneous and Cu(II)-Catalyzed Hydrolysis of Amides **1**–**7**[a]

no.	compd	k_{OH},[b] M^{-1} s^{-1}	k_{OH}^{Cu},[c] M^{-1} s^{-1}	pH (buffer)[d]	REF[e]
1		3.78×10^{-6}	1660	5.7–6.2 (MES)	4.4×10^{8}
2		2.02×10^{-6}	*f*	5.5–6.3 (MES)	
3		2.22×10^{-5}	224	5.9–6.4 (MES)	1.0×10^{7}
4		2.63×10^{-6}	*f*	4.2–4.7 (formate)	
5		1.31×10^{-5}	*g*	5.8–6.4 (MES)	
6		7.8×10^{-5}	175	5.9 (MES)	2×10^{6}
7		8.0×10^{-5}	370	6.0 (MES)	5×10^{6}

[a] Hydrolysis of **1**–**5** in H_2O–$HOCH_2CH_2OH$ (2:1) and **6** and **7** in H_2O was carried out at 50 °C, using 2 mM amide. k_{obs} values were determined from first-order plots to ≥4 half-lives (when $k_{obs} < 10^{-5}$ s^{-1}, initial rates method was used). [b] For **1**–**5**, the second-order k_{OH}'s were calculated from first-order k_{obs} data at pH 11–13, which gave a linear pH–rate plot with unit slope; K_w = 13.12 for H_2O–$HOCH_2CH_2OH$ (2:1, v/v) at 50 °C (Rondinini, S.; Longhi, P.; Mussini, P. R.; Mussini, T. *Pure Appl. Chem.* **1987**, *59*, 1693); reaction progress was monitored at 243 nm (238 nm for **4**). For **6** and **7**, k_{OH} values were calculated from first-order k_{obs} data (monitored at 350 nm) at 0.1 M NaOH (K_w = 13.26 for H_2O at 50 °C). [c] 2 mM $Cu(NO_3)_2$; 40 mM formate or MES buffer; μ = 0.1 M maintained with KNO_3 (KCl for **6** and **7**). Reaction progress was monitored at 300 nm for **1** and **3**–**5**, 310 nm for **2**, and 350 nm for **6** and **7**; reaction products were confirmed through TLC and ^1H NMR spectroscopy. For **1** and **3**, the second-order k_{OH}^{Cu} values represent the linear (slope = 1) portion of the pH–rate profile. For **6** and **7**, the k_{OH}^{Cu} values listed were calculated from the average of two or three k_{obs} measurements at a single pH value. [d] MES = morpholineethanesulfonate. pH was measured at 50 °C and required no correction for the mixed-solvent system (tested using $HClO_4$ dilutions). [e] Rate enhancement factor, the ratio of Cu(II)-catalyzed to uncatalyzed second-order k_{OH} values. Possible ionic strength difference effects are ignored. [f] No hydrolysis was detected in 72 h. [g] An upper limit for the first-order k_{obs} was established to be 2×10^{-7} s^{-1} over the pH range indicated, putting an upper limit of 1 M^{-1} s^{-1} for k_{OH}^{Cu} at pH 6.4.

(Pic-Gly, **2**).[12] In Figure 1 are shown pH–rate profiles for hydrolysis of Pic-Sar in the absence and presence of various concentrations of Cu(II) in water–$HOCH_2CH_2OH$ (2:1), where the cosolvent permitted obtaining rate data up to pH 6.2 without precipitation. The log k_{obs} vs pH slope is seen to approach unity near neutral pH, indicating that Cu(II) catalysis of the normal HO^--dependent hydrolysis is the predominant kinetic process in this pH range. The increase in rate with increasing [Cu(II)] is a consequence of incomplete saturation of the ligand using 1 equiv of Cu(II); however, a plot of $1/k_{obs}$ vs $1/[Cu(II)]$ at any given pH (not shown) yielded "saturation" k_{obs} values which were only ca. 5% higher than the 10 mM Cu(II) k_{obs} values plotted in Figure 1.

We also investigated *N*-(6-carboxypicolinyl)sarcosine, (6-COOH)Pic-Sar (**3**),[12] which is a better chelating agent and is essentially saturated with 1 equiv of Cu(II). To this we could compare the behavior of the isomer *N*-(2-carboxyisonicotinyl)-sarcosine (**5**),[12] which binds Cu(II) in a manner that provides electronic activation of the amide carbonyl (via pyridine coordination) in the same way as does (6-COOH)Pic-Sar, but without permitting direct interaction between Cu(II) and the scissile amide bond. The pH–rate profile for hydrolysis of (6-COOH)Pic-Sar using 1 equiv of Cu(II) is shown in Figure 2, where it is seen that log k_{obs} is nearly linear with increasing pH (slope = 1) in the highest pH range (5.8–6.4) we could study without precipitation. In contrast to (6-COOH)Pic-Sar, the isonicotinyl isomer **5** displayed a barely detectable hydrolysis in the presence of Cu(II). Thus, the major catalytic effect of Cu(II) involves direct interaction with the scissile amide group and not a through-resonance electrophilic activation.

Although the pH–rate profiles for Cu(II)-catalyzed hydrolysis of Pic-Sar and (6-COOH)Pic-Sar (Figures 1 and 2) become complicated at lower pH (a pH-independent kinetic term becomes important in the former case, as will be elaborated later), the essentially unit slopes in the near-neutral pH region can be directly compared to the unit slopes of the uncatalyzed HO^--dependent hydrolyses. The resulting REF ratios for these two compounds (Table I) are very large. The REF for Pic-Sar calculated using the 1-equiv Cu(II) data underestimates somewhat[14] what the optimal REF would be at saturation but is still larger than the REF obtained for (6-COOH)Pic-Sar. Thus, although the 6-COOH substituent improves binding of Cu(II), the additional coordination must weaken the catalytic "power" of Cu(II), presumably on account of diminished Lewis acidity.

In contrast to the cases of Pic-Sar and (6-COOH)Pic-Sar, no detectable hydrolysis of the corresponding *secondary* amides Pic-Gly (**2**) and (6-COOH)Pic-Gly (**4**)[12] was observed in the presence of 1 equiv of Cu(II) in the pH range free of precipitation problems (Table I). This observed hydrolytic inertness is the

(12) Compounds **1**–**4** and **6** were synthesized and characterized as previously described.[13] Compounds **5** and **7** are described in the supplementary material.

(13) Reddy, K. V.; Jin, S.-J.; Arora, P. K.; Sfeir, D. S.; Maloney, C. S. F.; Urbach, F. L.; Sayre, L. M. *J. Am. Chem. Soc.* **1990**, *112*, 2332.

(14) The true REF differs from our measured REF by a factor of $(1 + 1/K[Cu]_t)$, where K is K_{assoc} for Cu(II) + amide ⇌ Cu(II)·amide.

expected consequence of Cu(II)-induced amide NH deprotonation, previously demonstrated by us to occur with apparent pK_a values of 3.1-3.2 in these cases.[13,15]

Rate data were also obtained (Table I) for the Cu(II)-catalyzed and uncatalyzed basic hydrolysis of two 8-hydroxyquinoline-based systems,[12] where spectral titrations indicated essentially complete saturation with 1 equiv of Cu(II). In these cases we did not generate pH-rate profiles, so that the "single-point" REF values listed must be taken as upper estimates. Even so, these REFs are seen to be smaller than that observed for (6-COOH)Pic-Sar, indicating that the 8-hydroxyquinoline ligand provides a Cu(II) of suboptimal catalytic power, probably on account of diminished Lewis acidity and/or a deleterious chelate geometry.

In summary, we have shown that structurally simple, coordinating amides containing *aliphatic* amine leaving groups are subject to marked Cu(II) catalysis[16] of the normal HO^--dependent hydrolysis when amide NH deprotonation is blocked; the apparent REFs are at least as large as the 10^5-10^7 REFs we saw previously for *aromatic* amine leaving groups (anilides) using Cu(II).[17] As in the anilide case, we cannot here distinguish between kinetically equivalent metal hydroxide (intramolecular) and carbonyl activation (with external HO^- attack) mechanisms. Nonetheless, the magnitude of catalysis reported in Table I is comparable to what Groves and co-workers observed for specially designed aliphatic lactams which control the stereoelectronics of metal ion-carbonyl interaction,[8] suggesting that such constraints are not absolute requirements for observing large catalytic effects. It thus appears that amide hydrolysis is *intrinsically* subject to metal ion catalysis to a degree which rivals that seen for ester hydrolysis, a notion which is not generally appreciated.

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Registry No. **1**, 125686-77-3; **2**, 5616-29-5; **3**, 125686-83-1; **4**, 125686-80-8; **5**, 138878-36-1; **6**, 125686-79-5; **7**, 138878-37-2; H-Sar-OCH_2Ph·TsOH, 54384-06-4; Pic-Sar-OCH_2Ph, 138878-38-3; Cu(N-$O_3)_2$, 3251-23-8; bis(pyridine-2,6-dicarboxylic acid)copper(II), 68398-38-9; 8-hydroxyquinoline-2-carboxylic acid, 1571-30-8.

Supplementary Material Available: A textual presentation of experimental details (2 pages). Ordering information is given on any current masthead page.

(15) (6-COOH)Pic-Gly-Cu(II) exhibits a coupled 2-proton dissociation with pK_a = 3.20 and a third dissociation with pK_a = 5.48, but amide dissociation occurs in the former instance. The latter pK_a probably corresponds to "outside" protonation of the carbonyl oxygen in the amide-*N*-ligated tridentate complex.

(16) Since complete hydrolysis can be achieved using substoichiometric amounts of Cu(II) (the rate slows down at proportional percent reactions due to the more favorable binding of Cu(II) to products than to reactants), we prefer to speak of metal ion *catalysis* rather than metal ion *promotion* of hydrolysis.

(17) Reddy, K. V.; Jacobson, A. R.; Kung, J. I.; Sayre, L. M. *Inorg. Chem.* **1991**, *30*, 3520.

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EPR Studies of a Dinickel Complex in Its II,II and II,III Oxidation States

Bimetallic complexes of 2,6-bis[(bis(2-pyridylmethyl)amino)-methyl]-4-methylphenol (HMPMP) and related ligands have been found to exhibit a variety of interesting spectroscopic and magnetic properties.[1] The EPR spectra observed for these complexes have been useful in understanding the physical properties of diiron-oxo proteins in their diferrous and mixed-valence forms.[2] In turn, these complexes have in part allowed the development of a quantitative treatment of these signals.[3] The spectroscopic properties of model dinickel complexes are of interest[4] as models for the putative dinickel active site of jack bean urease.[5] In this communication, we report the detection of an integer-spin EPR signal from a $Ni^{II}Ni^{II}$ complex and the first observation of a half-integer-spin EPR signal from a mixed-valence $Ni^{II}Ni^{III}$ complex.

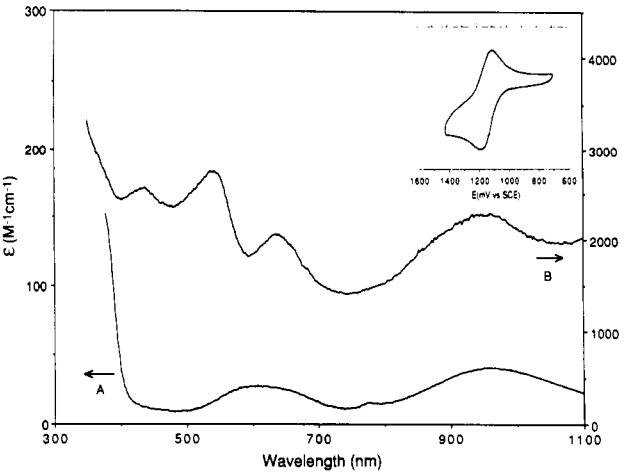

Figure 1. UV-vis absorption spectra of (A) **1** in CH_3CN at 23 °C and (B) **3** in CH_2Cl_2 at -50 °C. The cyclic voltammetry trace of **2** in CH_2Cl_2 is shown in the inset.

$[Ni_2BPMP(O_2CC_2H_5)_2]BPh_4·CH_3COCH_3$ (**1**) and $[Ni_2BPMP(O_2CCH_3)_2]ClO_4$ (**2**), obtained as pale blue crystals,[6] exhibit properties expected of complexes with (μ-phenoxo)bis(μ-carboxylato)dimetal cores such as $[Fe_2BPMP(O_2CC_2H_5)_2]BPh_4$.[1f]

(1) (a) Borovik, A. S.; Papaefthymiou, V.; Taylor, L. F.; Anderson, O. P.; Que, L., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 6183-6195. (b) Suzuki, M.; Uehara, A.; Oshio, H.; Endo, K.; Yanaga, M.; Kida, S.; Saito, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3547-3555. (c) Mashuta, M. S.; Webb, R. J.; Oberhausen, K. J.; Richardson, J. F.; Buchanan, R. M.; Hendrickson, D. N. *J. Am. Chem. Soc.* **1989**, *111*, 2745-2746. (d) Holman, T. R.; Andersen, K. A.; Anderson, O. P.; Hendrich, M.; Juarez-Garcia, C.; Münck, E.; Que, L., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 921-923. (e) Holman, T. R.; Juarez-Garcia, C.; Hendrich, M. P.; Que, L., Jr.; Munck, E. *J. Am. Chem. Soc.* **1990**, *112*, 7611-7618. (f) Borovik, A. S.; Hendrich, M. P.; Holman, T. R.; Munck, E.; Papaefthymiou, V.; Que, L., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 6031-6038.

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(5) (a) Dixon, N. E.; Gazzola, C.; Blakeley, R. L.; Zerner, B. *J. Am. Chem. Soc.* **1975**, *97*, 4131-4133. (b) Clark, P. A.; Wilcox, D. E. *Inorg. Chem.* **1989**, *28*, 1326-1333. (c) Clark, P. A.; Wilcox, D. E.; Scott, R. A. *Inorg. Chem.* **1990**, *29*, 579-581.

(6) Complex **1** was synthesized similarly to the $[Fe_2BPMP(\mu$-$O_2CC_2H_5)_2](BPh_4)_2$ complex. Anal. Calcd for $C_{66}H_{69}BN_6Ni_2O_6$: C, 67.72; H, 5.94; N, 7.18; Ni, 10.02. Found: C, 67.46; H, 6.08; N, 7.43; Ni, 9.68. The preparation of compound **2** involved the sequential addition of 2 equiv of $Ni(OAc)_2·4H_2O$ and 2 equiv of NEt_4ClO_4 to a methanolic solution of HBPMP. The resulting mixture slowly evaporated at 10 °C, yielding crystals (≈64%) which were spectroscopically identical to **1**. Anal. Calcd for $C_{37}H_{39}N_6ClNi_2O_9$: C, 51.40; H, 4.55; N, 9.72. Found: C, 51.35; H, 4.69; N, 9.48.

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