least-squares analysis is (8.3 ± 0.2) × 10^{-4} s^{-1}, which is in agreement with the value obtained for iodide, providing further evidence for a dissociative mechanism. The second reaction is independent of the nucleophile concentration with a rate constant of (1.4 ± 0.1) × 10^{-4} s^{-1}.

The concentration profile does not eliminate an associative pathway for the above equilibria involving aquation of the palladium center concurrent with loss of the halide. However, owing to the constrained "square-pyramidal" geometry of the Pd centers, it is viewed as unlikely that such an association would be favored. In view of the similarity of the k_a values in both the I^- and SCN^- substitution reactions, we postulate a rate-limiting dissociation of the bromide. It is possible that the presence of the second Pd acting as a "fifth" ligand provides the necessary stabilization of the transition state which would no longer be akin to the three-coordinate ion that must be formed in the monomeric reaction pathway.

Acknowledgment. We thank the NSERC and the University of Victoria for financial support. T.W.W. acknowledges the receipt of an NSERC Postgraduate Scholarship. We also wish to acknowledge the contribution of Mrs. K. Beveridge.

Supplementary Material Available: Tables S1-S16, containing crystallographic parameters, bond lengths, bond angles, atomic coordinates, temperature parameters, intermolecular distances, and mean planes and deviations for $Pd_2([18]aneN_6)Br_2 \cdot 4H_2O$ and $Pd_2([20]aneN_6)Br_2 \cdot H_2O$, and a contour plot of the 2-dimensional COSY spectrum for $Pd_2([20]aneN_6)Br_2^{2+}$ in D_2O (12 pages); Tables S17 and S18, listing structure factors for $Pd_2([18]aneN_6)Br_2 \cdot 4H_2O$ and $Pd_2([20]aneN_6)Br_2 \cdot H_2O$ (12 pages). Ordering information is given on any current masthead page.

Contribution from the Department of Chemistry,
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Divalent Metal Ion Catalyzed Hydrolysis of Picolinanilides[1]

K. Veera Reddy, Alan R. Jacobson, John I. Kung, and Lawrence M. Sayre*

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The hydrolysis of *N*-methylpicolinanilides bearing electron-withdrawing substituents (4-nitro, 2,4-dinitro, and 5-chloro-2-nitro) was studied as a function of pH at 40.0 °C in ethanol-water (1:2) in the absence and presence of divalent metal ions, in particular Cu(II). Plots of log *k* vs pH for *uncatalyzed* hydrolysis were linear with unit slope over the pH range 9-12, permitting the calculation of bimolecular k_{OH} values for this region. Plots of log *k* vs pH in the presence of various concentrations of Cu$(NO_3)_2$-bpy (1:1) increased linearly (slope = 1) over the pH range 5.0-6.2, plateaued over the pH region 7-9, and increased again at higher pH as the uncatalyzed reaction came to prominence. Catalysis by Cu(II) in the absence of bpy (for the 4-nitroanilide) could be followed only below pH 6, but log *k* increased linearly (slope = 1) in the pH range 4-6. The unit slope behavior at low pH for both the Cu^{II}(bpy)- and Cu^{II}-catalyzed reactions was interpreted in terms of Cu(II) catalysis of hydroxide-mediated hydrolysis. Second-order k_{OH}(Cu) values could be calculated from the unit slopes, which, when compared to the uncatalyzed k_{OH} values, indicate catalytic rate enhancements of 10^4-10^5 induced by 10 mM Cu^{II}(bpy). Saturation effects were seen for the 4-nitroanilide at high [Cu(II)] (±bpy), permitting an extrapolation to the maximum catalytic effect in these cases ((1-8) × 10^6). These catalytic factors are discussed in comparison to related systems studied by other workers.

Introduction

Despite the many studies carried out to elucidate the nature of metal ion catalysis of amide hydrolysis, the criteria that must be met for observing large catalytic rate enhancements and the mechanisms of the processes involved remain incompletely understood. In fact, it was believed at one time that hydrolysis of *simple* amides is not subject to large *catalytic*[2] effects of metal ions, in contrast to the situation with esters, where rate enhancements as large as 10^8 were observed.[3] This dichotomy was alleged to be a consequence of the fact that whereas ester hydrolysis follows a rate-limiting tetrahedral intermediate (TI) formation mechanism, amide hydrolysis generally follows a rate-limiting TI breakdown mechanism at pH ~ 7 due to the absence of a good leaving group.[4] In this way, the much greater rate accelerating effect of metal ions on ester hydrolysis than on amide hydrolysis might be ascribed to the expectation that a metal ion would have a greater catalytic effect on TI formation than on TI breakdown. According to this interpretation, the use of special amides where leaving group ability could be made as good as that of alkoxide should result in a switch to a rate-limiting TI formation mechanism, and pronounced metal ion catalysis should then be observed.

One straightforward approach to a systematic investigation of leaving group ability would be to employ substituted anilides, since the basic hydrolysis of *N*-alkyl anilides containing at least a *p*-nitro substituent is known to follow a rate-limiting TI formation pathway.[5] We chose *N*-methylpicolinanilides, where the pyridine N provides a coordination site for metal ions in a way that would encourage a carbonyl-activation and/or "metal hydroxide" mechanism and where the *N*-methyl group eliminated the chance of chelation-promoted NH deprotonation, which would generate a hydrolytically inert "amido" complex.[6] We chose to include 2,4-dinitro and 5-chloro-2-nitro substitution patterns since *o*-nitro has been found not only to retard TI formation as a consequence of steric inhibition of resonance but also to sterically accelerate TI breakdown, thus further assuring a rate-limiting TI formation mechanism.[7]

During our initial efforts,[8] Fife and Przystas published a study based on essentially the same premise, employing *N*-picolinylimidazoles.[9] These workers observed rate-enhancement factors

(1) This study was presented in preliminary form: Reddy, K. V.; Sayre, L. M. *Abstracts of Papers*, 199th National Meeting of the American Chemical Society, Boston, April 22-27, 1990; American Chemical Society: Washington, DC, 1990; INOR 189.

(2) Large rate enhancements have been seen for Co(III) systems (see: Sutton, P. A.; Buckingham, D. A. *Acc. Chem. Res.* **1987**, *20*, 357 and references cited therein), though the metal in these cases is stoichiometrically bound to the product, so that these reactions were considered to represent a metal ion *promoted* rather than metal ion catalyzed process.

(3) (a) Hay, R. W.; Morris, P. J. *Met. Ions Biol. Syst.* **1976**, *5*, 173. (b) Martell, A. E. *Met. Ions Biol. Syst.* **1973**, *2*, 207. (c) Hay, R. W.; Clark, C. R. *J. Chem. Soc., Dalton Trans.* **1977**, 1866, 1993. (d) Fife, T. H.; Przystas, T. J.; Squillacote, V. L. *J. Am. Chem. Soc.* **1979**, *101*, 3017.

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(5) Broxton, T. J. *Aust. J. Chem.* **1984**, *37*, 2005. Broxton, T. J.; Deady, L. W. *J. Org. Chem.* **1975**, *40*, 2906.

(6) (a) Grant, I. J.; Hay, R. W. *Aust. J. Chem.* **1965**, *18*, 1189. (b) Conley, H. L., Jr.; Martin, R. B. *J. Phys. Chem.* **1965**, *69*, 2914.

(7) (a) Skarzewski, J.; Aoki, M.; Sekiguchi, S. *J. Org. Chem.* **1982**, *47*, 1764. (b) Kajima, A.; Sekiguchi, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3597.

(8) Sayre, L. M.; Jacobson, A. R. *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.

(9) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1986**, *108*, 4631.

0020-1669/91/1330-3520$02.50/0

Table I. Effect of the Presence of the Nitrate Salts of Divalent Metal Ions on the Hydrolysis of Aryl-Substituted *N*-Methylpicolinanilides[a]

	$k_{obs}(+M^{II})/k_{obs}(-M^{II})$, 39.0 °C		
	4-NO_2	2,4-$(NO_2)_2$	5-Cl-2-NO_2
2 equiv Zn(II)	1.0 (pH 10)	33 (pH 8) 0.9 (pH 11)	6.0 (pH 8)
1 equiv Ni(II)	1.5 (pH 7) 0.9 (pH 11)	6 (pH 7)	
1 equiv Cu(II)	35 (pH 7) 2 (pH 11)	36 (pH 7)	

[a] Solvent is EtOH–water (1:2); $[anilide]_0$ = 0.2 mM; pH maintained with 7 mM PIPES (pH 7–8) or sodium tetraborate (pH 10–11).

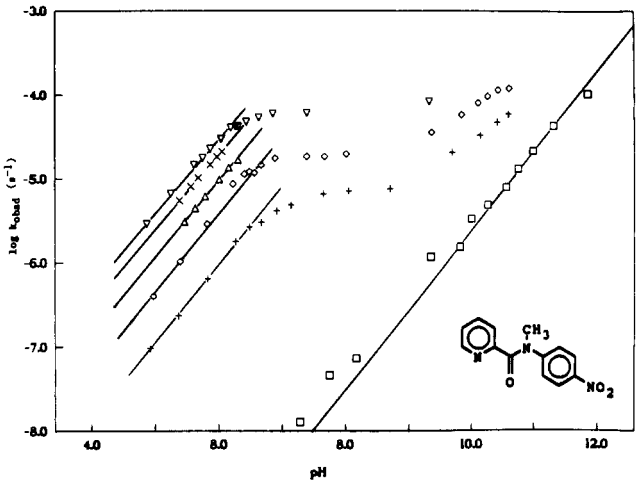
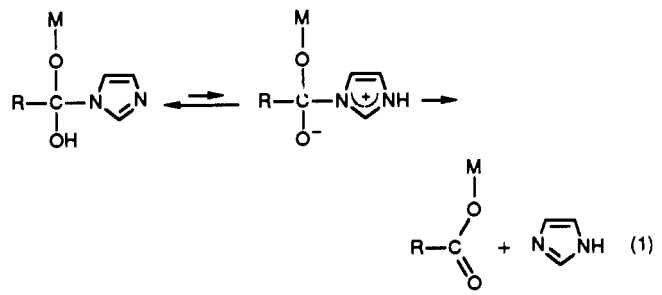


Figure 1. Plot of log k_{obsd} vs pH for hydrolysis of *N*-methyl-*N*-(4-nitrophenyl)picolinamide in EtOH–H_2O (1:2) at 40 °C with μ = 0.1 M (KNO_3), in the absence (□) and presence of Cu^{II}(bpy) at 0.2 (+), 1.0 (◇), 2.0 (△), 5.0 (×), and 10.0 (▽) mM.

(REFs) as large as 10^9 for Cu(II) catalysis, using a 6-carboxy substituent to ensure strong binding. Since this rate acceleration was so much higher than what had been observed previously for amides and in fact was on par with the largest catalytic effects observed for ester hydrolysis, we wondered whether this result was general or represented an idiosyncrasy of the imidazole leaving group. In the latter regard, one possibility that we considered was a tautomerization prior to C–N bond cleavage which would allow for expulsion of neutral imidazole (eq 1), from a dianionic



(1)

tetrahedral intermediate.[10] Since the anilides would not be capable of such tautomerization, a comparison of these rates with those obtained for the picolinylimidazoles would be of great interest.[11]

Results

Preliminary Studies. Representative data obtained on the effect of the presence of 1–2 equiv of Zn(II), Ni(II), or Cu(II) on the hydrolysis of three *N*-methylpicolinanilides (2-nitro, 2,4-dinitro, and 5-chloro-2-nitro) are given in Table I.[8] This limited data suggested that the largest catalytic effect was occurring in the case of Cu(II), as expected on the basis of it being the strongest Lewis acid. Further studies were restricted to a comparison of the uncatalyzed and Cu(II)-catalyzed hydrolysis.

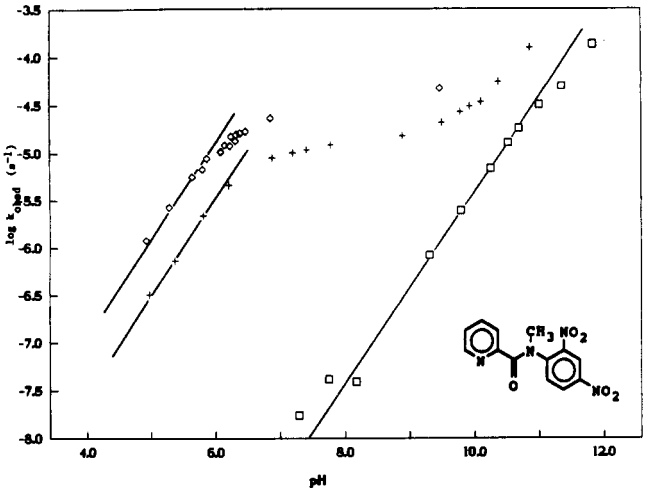


Figure 2. Plot of log k_{obsd} vs pH for hydrolysis of *N*-(2,4-dinitrophenyl)-*N*-methylpicolinamide in EtOH–H_2O (1:2) at 40 °C with μ = 0.1 M (KNO_3) in the absence (□) and presence of Cu^{II}(bpy) at 2.0 (+) and 10.0 (◇) mM.

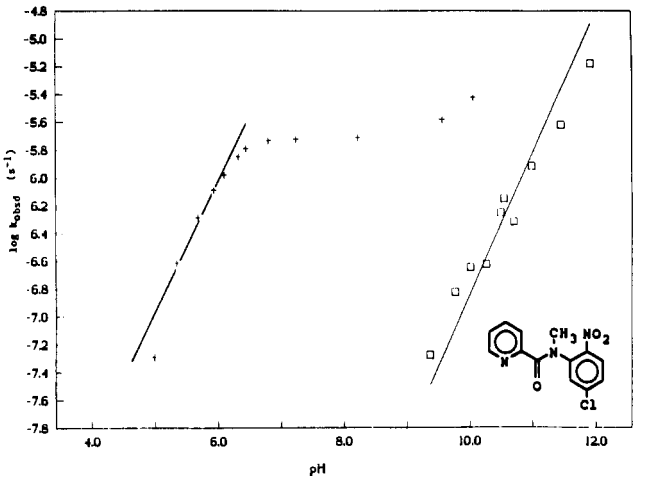


Figure 3. Plot of log k_{obsd} vs pH for hydrolysis of *N*-(5-chloro-2-nitrophenyl)-*N*-methylpicolinamide in EtOH–H_2O (1:2) at 40 °C with μ = 0.1 M (KNO_3), in the absence (□) and presence (+) of Cu^{II}(bpy) at 10.0 mM.

Alkaline Hydrolysis. The pH rate profiles for the uncatalyzed hydrolysis of the three anilides are included in Figures 1–3 (rightmost plot in each case) and are seen to be fairly linear over the pH range 9.5–12 with unit slope, though there is a hint of curvature at both higher and lower pH. Thus, the main reaction in operation in this pH range appears to be the normal first order in hydroxide type, although it is not possible to conclude whether formation or breakdown of the monoanionic tetrahedral intermediate is rate-limiting. Mechanistic variation in the alkaline hydrolysis of anilides has been studied in detail by several groups of workers,[4,5,7] and an extension of these studies to picolinanilides was not a major aim of the present study.

The second-order uncatalyzed rate constants (k_{OH}) obtained from the linear (slope = 1) portion of our pH–rate data are listed in Table II. The values for the 4-nitro and 2,4-dinitro compounds at 40 °C are about 100 times faster than the values of k_{OH} calculated[12] from the published data for hydrolysis of the cor-

(10) Decomposition of a dianionic tetrahedral intermediate, observed at high pH for the alkaline hydrolysis of certain anilides, is an abnormally rapid process.[4]

(11) A very recent study reported on the divalent metal ion catalyzed hydrolysis of amides of 2,4-dinitroaniline and 8-aminoquinoline: Przystas, T. J.; Fife, T. H. *J. Chem. Soc., Perkin Trans. 2* **1990**, 393.

(12) Calculated from $k_1k_2/(k_{-1} + k_2)$, neglecting the higher [HO^-] order term that becomes significant at high pH.

Table II. Bimolecular Rate Constants for the Uncatalyzed and Cu(II)-Catalyzed Alkaline Hydrolysis of *N*-Methylpicolinanilides in EtOH–Water (1:2) at 40.0 °C and μ = 0.1 M, $[\text{anilide}]_0$ = 0.2 mM

anilide	k_{OH}, M^{-1} s^{-1}	k_{OH}(Cu), M^{-1} s^{-1} ($[Cu^{II}]$)	REF[b]
5-Cl-2-NO_2	1.3×10^{-3}	1.0×10^{2} (10 mM Cu^{II}(bpy))	8.0×10^{4}
2,4-$(NO_2)_2$	4.1×10^{-2}	1.3×10^{3} (10 mM Cu^{II}(bpy))	3.2×10^{4}
4-NO_2	2.28×10^{-2}	3.8×10^{3} (10 mM Cu^{II}(bpy))	1.7×10^{5}
		2.4×10^{4} (satd[a] Cu^{II}(bpy))	1.0×10^{6}
		6.2×10^{4} (8 mM Cu^{II})	2.7×10^{6}
		1.9×10^{5} (satd[a] Cu^{II})	8.2×10^{6}

[a] These are extrapolated rates representing saturation of the *N*-methylpicolinanilide with Cu(II), obtained from the intercept of the reciprocal plots (least-squares fit) shown in Figures 5 and 6. [b] Rate-enhancement factor (dimensionless) on the bimolecular k_{OH} resulting from the presence of Cu(II) or Cu^{II}(bpy).

responding secondary acetanilides at 30 °C: 2.24×10^{-4} M^{-1} s^{-1} for $CH_3CONHC_6H_4NO_2$ (ref 4a) and 4.60×10^{-4} M^{-1} s^{-1} for $CH_3CONHC_6H_3(NO_2)_2$ (ref 7a). The temperature difference can account for only part of this difference, suggesting that the electron-withdrawing effect of the pyridyl moiety is providing an appreciable rate acceleration. Interestingly, from previous work on acetanilides, it is known that the greater rate of 2,4-dinitro relative to 4-nitro is a consequence of a greater partitioning of the TI toward C–N cleavage in the 2,4-dinitro case, since the TI formation rate for 2,4-dinitro is actually 5 times slower.[7a] Our observation that the 5-chloro-2-nitro compound hydrolyzes slowly relative to the two 4-nitro compounds may be because it lacks the 4-nitro-induced delocalization of the amide nitrogen, an absence which is not remedied by the 2-nitro group on account of steric inhibition of resonance. This results in a lower ground-state electrophilicity of the amide carbonyl and diminished stability of the aniline leaving group in the 5-chloro-2-nitro case.

Cu^{II}(bpy)-Catalyzed Hydrolysis. It was clear that binding of divalent metal ions to the picolinanilides was weak, so that the maximum catalytic effect would require high metal ion concentrations. Weak binding also meant that, using simple metal ion salts, kinetic studies would be permitted only over a lower pH range on account of precipitation of metal hydroxides at higher pH. In fact the early relative rate data we obtained (Table I) was calculated from initial rates prior to the development of precipitates. Homogeneity throughout the reaction in the case of excess $Cu(NO_3)_2$ could be attained only below pH 6.

In hoping that an ancillary ligand would permit kinetic data to be obtained over a wider range of pH and [Cu(II)], we settled on the use of 1 equiv 2,2′-bipyridine (bpy) per equiv Cu(II). We found that Cu^{II}(bpy) remained an effective catalyst (though less so compared to aquo Cu(II), vide infra), probably because of the π-back-bonding nature of the bpy ligand, which counteracts to some extent the decrease in Lewis acidity arising from σ-donation.

(a) With Phosphate Buffer. In our initial studies using Cu^{II}(bpy), we first attempted to obtain pH rate information using phosphate as a "universal" buffer. Although phosphate is notorious for complexing metal ions, we were curious to know if it could be used with Cu^{II}(bpy). In Figure 4 are shown data for the pH-dependent hydrolysis of 4-nitro-*N*-methylpicolinanilide using 60 mM phosphate buffer in the absence of metal ion and in the presence of 0.2 and 2 mM Cu^{II}(bpy) (1 and 10 equiv, respectively, based on anilide). The small effect of Cu(II) seen here and its decreased effectiveness at high pH (the rates approach those of the uncatalyzed reaction) suggested to us that binding of phosphate to Cu(II), which would be especially prevalent at high pH, might be detracting from its catalytic effect. To check this, we carried out a few kinetic runs over the pH range 7.8–9.2 using 2 mM Cu^{II}(bpy) and various phosphate buffer concentrations. The rates exhibited a linear (nearly unit slope) increase in log k with increasing pH in this range (data not shown) but *decreased* in magnitude with increasing phosphate concentration. The k_{OH} values (M^{-1} s^{-1}) calculated for the Cu(II)-catalyzed basic hydrolysis were 0.51, 0.14, and 0.091 for phosphate concentrations of 5, 20, and 60 mM (μ was maintained at 0.10 M with KNO_3).

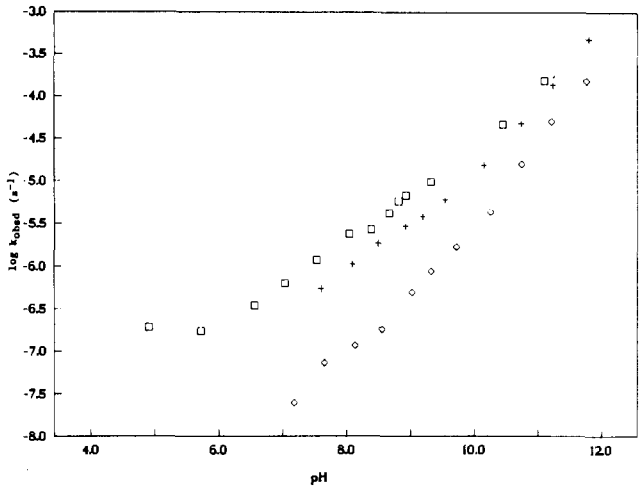


Figure 4. Plot of log k_{obsd} vs pH for hydrolysis of *N*-methyl-*N*-(4-nitrophenyl)picolinamide in EtOH–H_2O (1:2) using 60 mM potassium phosphate buffer at 40 °C with μ = 0.1 M (KNO_3), in the absence (□) and presence of Cu^{II}(bpy) at 0.2 (+) and 2.0 (◇) mM.

It is clear that phosphate is inhibitory to the Cu(II)-catalyzed reaction.

(b) With Noncoordinating Buffers. For the remainder of our studies, we used a combination of formate, acetate, MES, HEPES, and borate buffers, as done by other workers in the field. In the case of borate (H_3BO_3 + KOH) used at high pH, we performed a limited number of control studies to ensure an inert role of this particular buffer. Using a constant μ = 0.1 M maintained with KNO_3, we found that the rate of hydrolysis of the 4-nitro compound at pH 10.5, 40 °C, in the presence of 0.2 mM Cu^{II}(bpy) was 4.42×10^{-5} and 4.58×10^{-5} s^{-1} for [borate] = 5 and 100 mM, respectively, indicating an insignificant effect of the buffer. In addition, with use of [borate] = 5 mM at pH 10, the rate of hydrolysis of the 4-nitro compound using several concentrations of Cu^{II}(bpy) (0.2–2 mM) was found to change little as the overall ionic strength was varied from 5 to 100 mM (data not shown). Lastly, we showed that, in the overlapping pH range (6.7–6.8) of use of the two "non-coordinating" buffers HEPES and MES, there was no significant variation in rate between the two buffers. Thus, although effects of buffer and ionic strength have been noted previously for amide hydrolysis under certain circumstances, these factors do not appear to have a major importance in the present study and will not be discussed further.

The pH rate profiles for hydrolysis of the three anilides in the presence of various concentrations of Cu^{II}(bpy) are shown in Figures 1–3 relative to the uncatalyzed (basic hydrolysis) plots. All reactions followed simple pseudo-first-order kinetics with linearity to >4 half-lives. This being observed even at 1:1 Cu(II):anilide, indicating a lack of inhibition by the picolinate product, suggests that we are witnessing *catalysis* rather than a *promotion* by Cu(II). The pH rate profiles for the Cu^{II}(bpy)-catalyzed reactions are complex, in that although the expected unit slope behavior at lower pH (5.0–6.2) is seen, log k was observed to plateau over the pH range of ~6 to ~9 and, at higher pH, the rate again increased with increasing pH, with asymptotic approach to the uncatalyzed pH–rate line. The accelerating effect of Cu^{II}(bpy) in the lower pH regimes increases with increasing concentration of the catalyst, as shown in Figures 1 and 2. Also, the inflections in the pH range 6–9 are seen to shift slightly to lower pH with increasing Cu(II)–anilide stoichiometry.

The rate-enhancing effect of Cu^{II}(bpy) for the three anilides was estimated in each case by comparing the left-hand, linear portion (slope = 1) of the pH–rate profiles at 10 mM Cu^{II}(bpy) (50-fold over anilide) to the parallel pH–rate profile of the "uncatalyzed" basic hydrolysis (listed as k_{OH}(Cu) and k_{OH} in Table II). This comparison ensures that we are relating the rates of two processes of identical kinetic form (slope of 1 corresponds to a hydroxide-dependent reaction in both cases). The resulting rate-enhancement factors (REFs, Table II) are somewhat less than

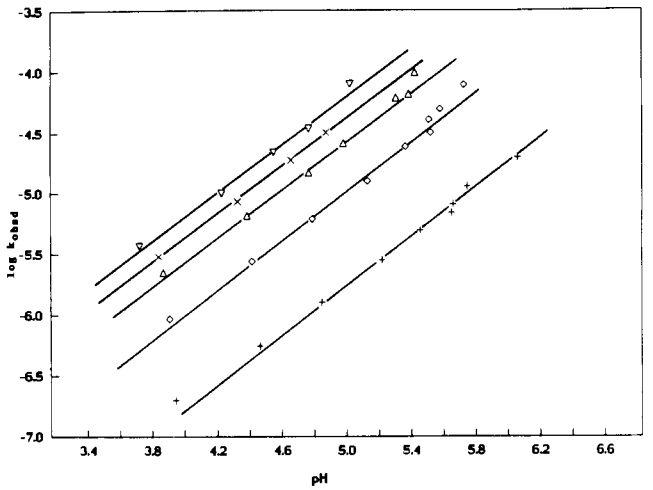


Figure 5. Plot of log k_{obsd} vs pH for hydrolysis of *N*-methyl-*N*-(4-nitrophenyl)picolinamide in EtOH–H_2O (1:2) at 40 °C with μ = 0.1 M (KNO_3), in the presence of $Cu(NO_3)_2$ at 0.2 (+), 1.0 (◇), 3.0 (△), 5.0 (×), and 8.0 (▽) mM.

the optimal catalytic factors on account of the fact that even at the 10 mM concentration of Cu^{II}(bpy), the anilide is incompletely bound. Interestingly, the k_{OH}(Cu) rank order does not exactly parallel that of k_{OH}. In particular, although base hydrolysis of the 2,4-dinitro compound is faster than that of the 4-nitro compound, the Cu(II)-mediated hydrolysis is slower (the REF is smaller by a factor of 5–6). This reversal could be due to the altered TI partitioning by the 2-nitro group discussed above.[7a]

Cu^{II}-Catalyzed Hydrolysis. Our utilization of Cu^{II}(bpy) as catalyst was based on our desire to measure hydrolysis rates over a wide pH region, including pH values of 7 and above, where precipitation of copper hydroxides would otherwise occur. Our finding that the most catalytically relevant part of the pH–rate profile fell in the slightly acidic range suggested that we could examine catalysis by Cu(II) itself in this range. Rate data for the hydrolysis of the 4-nitro compound was obtained over a range of pH and [Cu(II)] and was found to fit to a family of linear (slope = 1) pH rate plots, shown in Figure 5. The highest [Cu(II)] we could use without problems of precipitation was 8 mM, and the corresponding REF (Table II) was observed to be 16 times greater than that achieved with 10 mM Cu^{II}(bpy). This indicates, not surprisingly, that the complexation of Cu(II) by bpy significantly diminishes its catalytic potency. At the lowest [Cu(II)] (0.2 mM), we were able to obtain rate data in the absence of ethanol (water, trace CH_3CN; W. Tang and L. M. Sayre, to be published elsewhere), which yielded k_{obsd} values nearly identical with those obtained at 0.2 mM Cu(II) in water–ethanol (lowest line in Figure 5). This suggests that the observed kinetic behavior is not a consequence of the presence of ethanol. Furthermore, in water (trace CH_3CN) at 0.2 mM Cu(II), we were able to follow the rate up to pH 6.8, in which case an inflection was apparent at pH ~ 6.6, analogous to what we observed using Cu^{II}(bpy) (Figures 1–3). This suggests that the pH–rate profile inflections are general and are not an idiosyncrasy of Cu^{II}(bpy).

Saturation Effects. For the 4-nitro compound, we examined the question of possible saturation of the anilide substrate at high [Cu(II)] (±bpy), by plotting k_{OH} values calculated from the unit slope pH–rate dependencies of Figure 1 (low pH regime) and Figure 5 against [Cu(II)] (Figures 6 and 7). The curvature of these plots at the high [Cu(II)] end indicates that saturation is starting to occur; the rightmost point corresponds to 10 mM (50-fold over anilide) in the case of Cu^{II}(bpy) and 8 mM (40-fold over anilide) in the case of Cu(II) itself. From the reciprocal plots $1/k$ vs $1/$[Cu(II)] (Figures 6 and 7 insets), limiting values of k_{OH}(Cu) could be obtained by linear regression (Table II) that represent the rate for hydrolysis of the anilide when bound fully to either Cu^{II}(bpy) or Cu(II) itself. The intercept is further from the origin in the latter case (and is thus more accurate), where binding to amide substrate is expected to be stronger on account

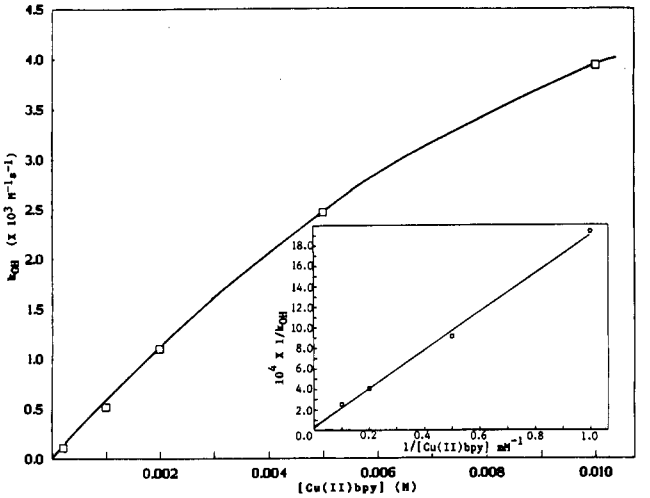


Figure 6. Plot of calculated second-order k_{OH} for the Cu^{II}(bpy)-catalyzed hydrolysis of *N*-methyl-*N*-(4-nitrophenyl)picolinamide as a function of catalyst concentration in EtOH–H_2O (1:2) at 40 °C with μ = 0.1 M (KNO_3). Inset is a reciprocal plot of the same data (least-squares fit, r = 0.997).

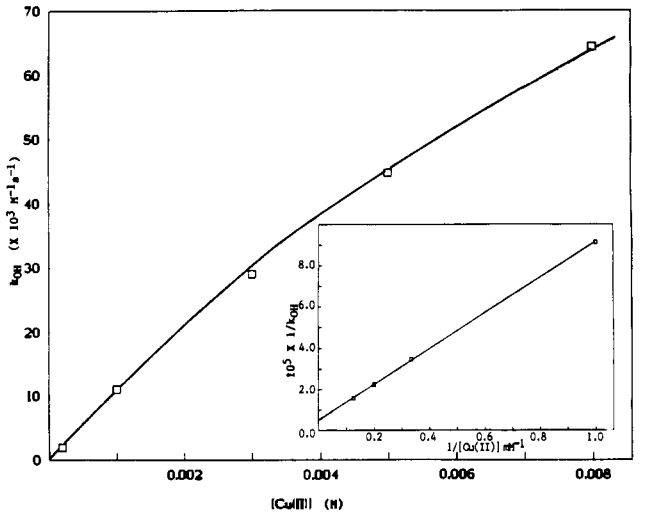


Figure 7. Plot of calculated second-order k_{OH} for the $Cu(NO_3)_2$-catalyzed hydrolysis of *N*-methyl-*N*-(4-nitrophenyl)picolinamide as a function of catalyst concentration in EtOH–H_2O (1:2) at 40 °C with μ = 0.1 M (KNO_3). Inset is a reciprocal plot of the same data (least-squares fit, r = 0.9998).

of undiminished Lewis acidity. The limiting REFs for k_{OH} are seen to be about 6× and 3× those of the REFs for 10 mM Cu^{II}(bpy) and 8 mM Cu(II), respectively.

Discussion

The sigmoidal pH–rate profiles shown in Figures 1–3 are reminiscent of those obtained by Groves and co-workers for the Cu(II)-mediated hydrolysis of ligand-functionalized aliphatic lactams.[13] In these cases, Cu(II) is coordinated stoichiometrically, and the conversion of a pH-dependent reaction at low pH to a nearly pH-independent reaction at pH ~ 7 was interpreted in terms of titration of the copper-bound water with a pK_a in this range. The pH-dependent reaction was proposed to involve intramolecular nucleophilic attack of Cu(II)–OH on the scissile amide carbonyl, which would not increase in rate once the copper-bound water was fully titrated. We propose a similar explanation to rationalize the inflections at pH 6–7 in Figures 1–3. Thus, we believe that the unit slope behavior in the pH rate profiles for both Cu^{II}(bpy) (Figures 1–3, low pH) and Cu(II) (Figure 5) represents an intramolecular Cu(II)–OH reaction (eq 2A) or the

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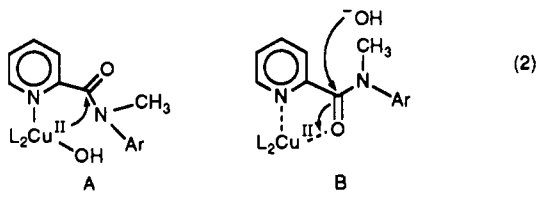

(2)

kinetically equivalent mechanism of external HO^- attack on an activated carbonyl (eq 2B). A mechanistic analysis of the full pH–rate profiles shown in Figures 1–3 in terms of various possible hydrolytic kinetic terms, as done by Groves and co-workers,[13] would be a difficult task in our case on account of the fact that our ligands are not saturated with Cu(II). Suffice it to say that the lack of saturation can be mathematically shown to be consistent with the observed shift of the pH inflection to lower pH with increasing Cu(II)–anilide stoichiometry (see Figure 1).

For the sake of argument, it should be pointed out that because the picolinanilides are not saturated with Cu(II), the pH dependence of k_{obsd} at low pH can be alternatively explained in terms of competition between Cu(II) and protons for binding to the pyridyl nitrogen, with the pH inflection then representing the pK_a of the pyridyl nitrogen conjugate acid in the solvent employed. We do not favor this interpretation for two reasons. First, the pyridyl pK_a in simple picolinamides has been found to be about 4 (W. Tang and L. M. Sayre, unpublished; see also ref 14). Second, we are presently investigating Cu(II)-mediated hydrolysis of the corresponding 6-carboxy-substituted *N*-methylpicolinanilides, in which cases saturation can be easily achieved. A mechanistic analysis of the pH–rate profiles in terms of multiple kinetic terms will be reported later for these cases, but preliminary data indicates that the 6-carboxy compounds follow pH–rate profiles similar to those shown in Figures 1–3. Thus, we feel confident that the unit slope log k vs pH dependence corresponds to Cu(II) catalysis of basic hydrolysis.

A pH-dependent (unit slope) reaction was previously observed by Fife and Przystas for the Cu(II)-mediated hydrolysis of picolinyl- and (6-carboxypicolinyl)imidazoles and was interpreted in terms of the same mechanistic dichotomy as that shown in eq 2,[9] though, in their case, the mechanism of eq 2B could be ruled out on the basis that the required second-order rate constant would be faster than the diffusion-controlled limit. Since the latter is not true in the present study, we cannot state a preference for either a carbonyl activation or a Cu–OH mechanism. The absolute rates of the uncatalyzed and Cu(II)-catalyzed hydrolysis of *N*-picolinylimidazole at 30 °C[9] are 10^5–10^6 times faster than what we observed for the nitro-substituted anilides at 40 °C. This does not appear to be a consequence of differing leaving group ability, assuming a common anion leaving group mechanism,[15] and may thus be indicative of a unique mechanism that allows for neutral leaving imidazole, as depicted in eq 1.

The rate enhancement factors (REFs) observed here are unprecedented for simple anilide substrates of this type. Our maximal REF for the 4-nitro compound of 8×10^6 (extrapolated to saturating [Cu^{II}]) is larger than the REF of 4×10^5 observed by Fife and Przystas for *N*-picolinylimidazole at 1 mM Cu^{II} (a saturating REF was not obtained in this case)[9] but is clearly smaller than the REF of $\sim 10^9$ observed by these workers for hydrolysis of *N*-(6-carboxypicolinyl)benzimidazole, which *is* saturated at 1 mM Cu^{II}. The REFs reported by Groves and co-workers for hydrolysis of 1:1 Cu(II) complexes of ligand-functionalized aliphatic lactams were 9.0×10^5 (ref 13a) and 1.6×10^6 (ref 13b). Clearly, our REFs are as large as these values, suggesting that the magnitude of Cu(II) catalysis does not vary that much between amides and anilides. The picolinyl systems, studied here and elsewhere,[9,11] may be subject to a special electronic activation of carbonyl on account of coordination of the metal ion to the pyridine nitrogen. If so, then the systems studied by Groves and co-workers may be more "pure" in the sense of relevance to peptides. However, the absence of observed catalysis for the isomeric but resonance-equivalent pyridine systems, *N*-(isonicotinyl)benzimidazole[9] and the 2-carboxyisonicotinamides studied in our lab,[16] suggests that the through-bond *electronic* advantage of metal ion coordination to the pyridine nitrogen is not a major contributor to the observed rate enhancements.

We recently argued that the observation of a large catalytic effect of metal ions on amide hydrolysis requires a facilitation of TI breakdown (C–N cleavage) as much as it does a facilitation of TI formation.[17] Thus, it was felt that a distinction between a carbonyl-activation and metal-hydroxide mechanism (both TI formation steps) may not address the most crucial question of catalytic mechanism. The REF data obtained on the present series of anilides, which are uncomplicated by ancillary catalytic factors such as intramolecular and/or buffer catalysis, suggests that special structural features are not required for the observation of large rate accelerations of amide hydrolysis by metal ions. Furthermore, in contrast to the view expressed by some workers, it appears that metal ions can exert as large a catalytic effect in the hydrolysis of simple amides, as in the case of simple esters.

Experimental Section

General. ^1H NMR spectra were recorded on a Varian XL-200 instrument, and chemical shifts are reported relative to tetramethylsilane. High-resolution mass spectra (HRMS) were obtained by using a Kratos MS-25 instrument. Melting points are uncorrected. The water used in the kinetics experiments was doubly distilled in an all-glass apparatus. Inorganic reagents were ACS grade. *N*-Methyl-4-nitroaniline was from Aldrich Chemical Co. 2,4-Dinitro-*N*-methylaniline[18] and 5-chloro-*N*-methyl-2-nitroaniline[19] were prepared and characterized as described. The ^1H NMR of the latter compound was not previously reported: ($CDCl_3$) δ 2.99 (d, 3 H, J = 5.15 Hz, NCH_3), 6.59 (dd, 1 H, J = 2.0 and 9.0 Hz, C_4–H), 6.80 (d, 1 H, J = 2.0 Hz, C_6–H), 8.05 (br s, 1 H, NH), 8.09 (d, 1 H, J = 9.0 Hz, C_3–H).

General Method for the Preparation of Picolinanilides. A mixture of picolinyl chloride–hydrochloride (1 mmol, 1.78 g) and 1 mmol of the appropriate *N*-methylaniline (1.52 g, 4-nitro; 1.87 g, 5-chloro-2-nitro; 1.97 g, 2,4-dinitro) was refluxed in 100 mL of benzene for 24 h under dry N_2 in the presence of 2.5 mmol of Et_3N (2.5 g). The solid that separated on cooling to room temperature was filtered off, the filtrate was evaporated in vacuo, and the residue was partitioned between $CHCl_3$ and half-saturated aqueous $NaHCO_3$. The crude product obtained upon evaporation of the organic layer was purified by silica gel column chromatography (EtOAc–$CHCl_3$, 1:1) to give the desired anilide in 70–80% yield.

***N*-Methyl-*N*-(4-nitrophenyl)picolinamide**: Yellow needles from methanol–water (3:1), mp 124 °C; ^1H NMR ($CDCl_3$) δ 3.58 (s, 3 H, NCH_3), 7.21 (d, 2 H, J = 8.9 Hz, Ar C_2/C_6–H), 7.27 (m, 1 H, Py C_5–H), 7.75 (m, 2 H, Py C_3/C_4–H), 8.11 (d, 2 H, J = 8.9 Hz, Ar C_3/C_5–H), 8.30 (d, 1 H, J = 4.7 Hz, Py C_6–H); HRMS (15 eV) m/z calcd for $C_{13}H_{11}N_3O_3$ (M^+) 257.0800, obsd 257.0797.

***N*-(5-Chloro-2-nitrophenyl)-*N*-methylpicolinamide**: Green needles from methanol–water (3:1), mp 64 °C; ^1H NMR ($CDCl_3$) δ 3.51 (s, 3 H, NCH_3), 7.19 (m, 1 H), 7.35 (m, 2 H), 7.73 (m, 1 H), 7.86 (m, 2 H), 8.12 (d, 1 H, J = 4.3 Hz, Py C_6–H); HRMS (15 eV) m/z calcd for $C_{13}H_{10}ClN_3O_3$ (MH^+, ^{35}Cl) 292.0488, obsd 292.0494.

***N*-(2,4-Dinitrophenyl)-*N*-methylpicolinamide**: Pale yellow needles from water–ethanol–ether (2:1:2), mp 82 °C; ^1H NMR ($CDCl_3$) δ 3.57 (s, 3 H, NCH_3), 7.25 (m, 1 H), 7.59 (d, 1 H, J = 8.7 Hz, Ar C_6–H), 7.79 (br t, 1 H), 7.93 (br d, 1 H), 8.16 (br d, 1 H, Py C_6–H), 8.43 (dd, 1 H, J = 2.2 and 8.7 Hz, Ar C_5–H), 8.80 (d, 1 H, J = 2.2 Hz, Ar C_3–H); HRMS (15 eV) m/z calcd for $C_{13}H_{10}N_4O_5$ (MH^+) 303.0729, obsd 303.0733.

Kinetics. Buffer solutions at various pH values were prepared weekly in doubly distilled water. The buffers used were as follows: formate (pH 3.5–4.7), acetate (pH 4.7–5.8), MES (pH 5.5–6.7), HEPES (pH 6.8–8.2), borate (pH 8.5–12.0). The ionic strength was maintained at

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0.1 M with KNO_3. Solutions of picolinanilides (6×10^{-4} M) were prepared in absolute ethanol and were used fresh. The 1:1 Cu(II)-bpy complex was prepared by dissolving equimolar quantities of $Cu(NO_3)_2$ and bipyridine and 2.5 equiv H_2O in absolute ethanol, followed by evaporation to give a blue solid, and aqueous solutions of this solid (2×10^{-4} to 1×10^{-3} M) were employed in the metal ion catalyzed hydrolyses. The apparent pH values of the reaction mixtures were obtained at 40.0 °C by using a Fisher Accumet Model 810 meter and were corrected to the operational pH values by subtracting 0.06, the appropriate value of δ for 28% (by weight) aqueous ethanol at 298 °C (the required additional correction for 313 °C vs 298 °C would be in the third decimal, beyond the accuracy of our pH measurements).[20]

Hydrolysis reactions were carried out in 1-cm quartz cells kept at constant temperature (40.0 °C) by using a Perkin-Elmer Lambda 3B UV-vis spectrophotometer (with PECSS software) equipped with a temperature-controlled six-cell changer. The progress of reaction was monitored by following the increase in absorbance of the product anilines at their characteristic band maxima: 400 nm for (4-nitrophenyl)- and (2,4-dinitrophenyl)-*N*-methylaniline and 430 nm for (5-chloro-2-nitrophenyl)-*N*-methylaniline. In a typical reaction, 1 mL of the appropriate picolinanilide ethanolic solution was added to 2 mL of the buffer solution (with or without metal ion) maintained at 40 °C. The products and extent of hydrolysis were confirmed by TLC. For the faster reactions, first-order linearity was confirmed to at least 4 half-lives. The final spectrum in these cases exactly matched that of an equimolar mixture of picolinic acid and the appropriate substituted *N*-methylaniline (with the proper amount of Cu(II) catalyst added). For the very slow reactions, k_{obsd} was determined from the initial rate (in some cases only 1-2% reaction) by using the equation $\ln (A_\infty - A_0)/(A_\infty - A_t) = kt$. Calculation of k_{OH} values from the pH-rate data was performed by using $\log K_w = -14.04$, estimated by interpolation of $\log K_w$ values for various ethanol-water mixtures reported by Gutbezahl and Grunwald at 25.0 °C,[21] with correction, as done by these workers, to 40.0 °C using the same temperature coefficient measured in water.[22]

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Registry No. bpy, 366-18-7; $Cu(NO_3)_2$, 3251-23-8; picolinyl chloride, 29745-44-6; 4-nitro-*N*-methylaniline, 100-15-2; 5-chloro-2-nitro-*N*-methylaniline, 35966-84-8; 2,4-dinitro-*N*-methylaniline, 2044-88-4; *N*-methyl-*N*-(4-nitrophenyl)picolinamide, 134847-69-1; *N*-(2,4-dinitrophenyl)-*N*-methylpicolinamide, 134847-70-4; *N*-(5-chloro-2-nitrophenyl)-*N*-methylpicolinamide, 134847-71-5.

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Effect of Cyclohexylene Bridges on the Metal Ion Size Based Selectivity of Ligands in Aqueous Solution

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The effect on thermodynamic complex stability of use of the cyclohexylene bridge in place of ethylene bridges in various types of ligands is investigated. The synthesis of THEDACH [*N,N,N',N'*-tetrakis(2-hydroxyethyl)-*trans*-1,2-diaminocyclohexane] is reported, along with that of 7,16-bis(*trans*-2-hydroxycyclohexyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (Cy_2-K22). The formation constants of these ligands, as well as of BHEAC [*trans*-1-(bis(2-hydroxyethyl)amino)-2-hydroxycyclohexane], for complex formation with some or all of the metal ions Cu(II), Zn(II), Cd(II), Pb(II), Ca(II), Sr(II), Ba(II), La(III), Th(IV), and Ag(I) are reported, determined by glass electrode potentiometry in 0.1 M $NaNO_3$ at 25 °C. The results indicate that the presence of a cyclohexylene bridge leads to complex stabilization relative to the analogues with ethylene bridges, which appears to be dependent on the size of the metal ion. The complexes of small metal ions are stabilized by the cyclohexylene bridge, whereas those of larger metal ions tend to be destabilized.

Replacement of the ethylene bridge connecting the two nitrogen donors of EDTA (Figure 1) with a cyclohexylene bridge leads to substantial increases in complex stability,[1] as measured by the formation constants, $\log K_1$, of the complexes formed for *trans*-CDTA (Figure 1; see also Chart I). This is an example[2] of "preorganisation",[3] in which it is thought[2] that the rigid cyclohexane ring of *trans*-CDTA holds its two nitrogens in the trans arrangement required for coordination to metal ions. In EDTA, by contrast, the low-energy form of the free ligand is thought to be the skew, and considerable energy must be expanded in transforming it to the trans form required for complex formation. It seemed that introduction of cyclohexylene groups as bridging groups in other chelating ligands would produce ligands of greatly increased complexing ability, and it was surprising that more ligands using the cyclohexylene bridge had not been synthesized.

The ligand THEEN (Figure 1) has an enhanced affinity for large metal ions relative to what is observed for EN, brought about by the presence of the 2-hydroxyethyl groups.[4] It was thought that by analogy with the case of CDTA, using *trans*-1,2-diaminocyclohexane rather than EN as the diamine to which 2-hydroxyethyl groups would be added would give THEDACH, a much more powerfully coordinating ligand than THEEN. As a further exploration of this idea, the ligand Cy_2-K22 was studied (Figure 1). This ligand has cyclohexylene groups bridging the nitrogen donors of the macrocyclic ring and the pendant alcoholic oxygen donors. This might give interesting effects on complex stability as compared with the case of BHE-K22, which has simple ethylene bridges linking the donor atoms of the pendant "arms" to the nitrogens of the macrocyclic ring.

It is found[1] that a cis conformation of the amines on the cyclohexylene group, as in *cis*-CDTA, leads to incorrect orientation of the nitrogen donor atoms for coordination to metal ions, and *cis*-CDTA shows little increase in complex stability as compared with EDTA. It is thus important that the hydroxyl group be trans to the nitrogen donors in Cy_2-K22. The method of synthesis employed here was the same as for many other nitrogen donor macrocycles with hydroxyalkyl pendant donor groups, namely

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