Contribution from the Nesmeyanov Institute of Organoelement Compounds, Vavilova 28, Moscow, USSR

Copper(II) Ion Promoted Direct Hydrolysis of 2-Cyanopyridine to Picolinic Acid. Intramolecular Catalysis by the Coordinated *N*-β-Hydroxyethyl Group

Yuri N. Belokon',* Vitali I. Tararov, Tatiana F. Savel'eva, Sergei V. Vitt, Elena A. Paskonova, Saltan Ch. Dotdayev, Yuri A. Borisov, Yuri T. Struchkov, Andrei S. Batasanov, and Vasili M. Belikov

Received June 10, 1988

Hydrolysis of 2-cyanopyridine to picolinamide was accelerated 100–300-fold, as compared with spontaneous hydrolysis, in the presence of a complex formed from Cu(II) ion and (*S*)-1-benzyl-2-[(ethylamino)methyl]pyrrolidine at 30 °C and pH 6–9.5 in H_2O. The rate enhancement was attributed to the intramolecular attack of coordinated hydroxide ion at the cyano group of the coordinated cyanopyridine. No picolinic acid was detected in the reaction mixture. But the copper(II)-catalyzed 2-cyanopyridine hydrolysis in the presence of (*S*)-1-benzyl-2-[((2-hydroxyethyl)amino)methyl]pyrrolidine produced, in addition to picolinamide, about 30–60% of picolinic acid. No hydrolysis of picolinamide to picolinic acid was observed under the experimental conditions. The formation of picolinamide and of picolinic acid followed different pathways, the latter being a typical consecutive two-stage type reaction with a buildup of an intermediate complex. The hydrolysis of 2-cyanopyridine to picolinic acid is considered to result from the initial nucleophilic attack of the coordinated hydroxyethyl group at the cyano group of the coordinated cyanopyridine with the formation of an intermediate coordinated imino ester, which is in turn slowly hydrolyzed further to picolinic acid.

Introduction

Transition metal ion catalysis in the hydrolysis of esters, amides, and nitriles has been intensively studied since 1952,[1] and the field is far from being exhausted.[2] The reactions are thought to be convenient models to clarify the chemical factors governing some enzymic proteolytic reactions.[3] Also, a deeper understanding of the mechanistic details of the catalysis may eventually help in the design of artificial biomimetic catalytic systems based on transition-metal ions.

The ability of transition-metal ions to promote hydrolysis can be accounted for by the two alternative mechanisms A and B (Scheme I). Mechanism A implies hydroxide ion external attack on the coordinated substrate, whereas mechanism B operates via the intramolecular attack of the coordinated hydroxide ion on the coordinated substrate.[2] Hydration of amino nitriles coordinated to cobalt(III), leading to the corresponding amides, is a well-documented case of intramolecular catalysis[2a] (mechanism B).

This paper reports on the hydrolysis of 2-cyanopyridine (CP) in water, catalyzed by Cu(II) complexes formed by the metal ion and bidentate and tridentate ligands (L^1, L^2, L^3). Significant acceleration over spontaneous hydrolysis was observed, and if coordinated hydroxide ion is substituted by coordinated alkoxide, the reaction product is no longer picolinamide (PAM) but picolinic acid (PAC).

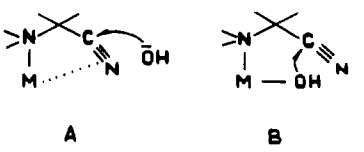
Results

Synthesis and Properties of the Ligands (L^1, L^2, L^3). The ligands were prepared according to the conventional procedures outlined in Scheme II, by starting from (*S*)-*N*-benzoylproline (**1**), the synthesis of which was described earlier.[4]

Spectral data and elemental analyses of L^1, L^2, and L^3 were in accord with the assigned structures.

Titration of the protonated forms of L^1, L^2, and L^3 revealed two equivalence points corresponding to two acid groups for each ligand. pK_a values were calculated by using the "Best" program[5] and are presented in Table I.

Scheme I



Scheme II

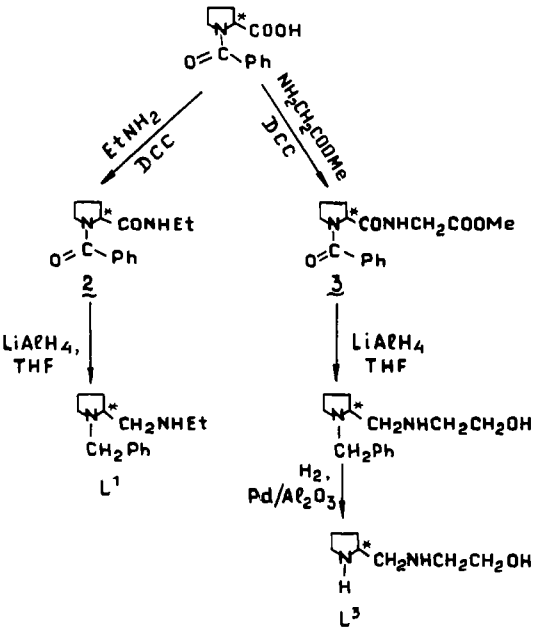


Table I. Ligand Acidity Constants[a]

ligand	pK_{a_1}	pK_{a_2}
L^1	5.87	9.81
L^2	5.60	9.18
L^3	6.36	10.11

[a] Measured at 30 °C in aqueous 0.1 M $NaNO_3$.

L^3 contains the most basic amino group that could be assigned to the unsubstituted pyrrolidine nitrogen atom (pK_a = 11.27 for the pyrrolidine[6]). As expected,[7a] L^2 is less basic than L^3, and L^1 is a stronger base than L^2 because the electronegative hydroxy

(1) Kroll, H. *J. Am. Chem. Soc.* **1952**, *74*, 2036.
(2) (a) Buckingham, D. A.; Morris, P.; Sargeson, A. M.; Zanella, A. *Inorg. Chem.* **1977**, *16*, 1910. (b) Groves, J. T.; Chambers, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 630. (c) Sigman, D. S.; Jorgensen, C. T. *J. Am. Chem. Soc.* **1972**, *94*, 1724. (d) Hay, R. W. In *Metal Ions in Biological Systems*; Sigel, H., Ed.; Marcel Dekker: New York, 1976; Vol. 5, p 173. (e) Wells, M. A.; Rogers, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1976**, *98*, 4336. (f) Brown, R. S.; Zamkaney, M.; Coho, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 5522. (g) Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 1041. (h) Hay, R. W.; Basak, A. K. *J. Chem. Soc., Dalton Trans.* **1986**, 39. (i) Hay, R. W.; Basak, A. K.; Pujari, M. P.; Perotti, A. *J. Chem. Soc., Dalton Trans.* **1986**, 2029.
(3) Valee, B. L. In *The Enzymes*, 2nd ed.; Boyer, P. D., Lardy, H., Myrbäck, K., Eds.; Academic: New York, 1960; Chapter 5.
(4) Baker, B. R.; Querry, M. V.; Kadish, A. F.; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 52.
(5) Motekaitis, R. J.; Martell, A. E. *Can. J. Chem.* **1982**, *60*, 2403.
(6) *CRC Handbook of Chemistry and Physics*, 62nd ed.; Weast, R. C., Ed.; CRC: Boca Raton, FL, 1981–1982; p D-139.
(7) (a) Ulanovski, I. L. Thesis; Moscow, 1985. (b) Courtney, R. C.; Gustafson, R. L.; Chaberec, S.; Martell, A. E. *J. Am. Chem. Soc.* **1959**, *81*, 519.

0020-1669/88/1327-4046$01.50/0

Scheme III

$$H_2L^{+2} \xrightleftharpoons{K_{a,1}} HL^{+} + H^{+}$$

$$HL^{+} \xrightleftharpoons{K_{a,2}} L + H^{+}$$

$$Cu^{+2} + L \xrightleftharpoons{K_{CuL}} CuL^{+2}$$

$$CuL^{+2} \xrightleftharpoons{K'_{a,1}} CuLH_{-1}^{+} + H^{+}$$

$$CuLH_{-1}^{+} \xrightleftharpoons{K'_{a,2}} CuLH_{-2} + H^{+}$$

$$Cu^{+2} + 2L \xrightleftharpoons{K_{CuL_2}} CuL_2^{+2}$$

Table II. Formation and Acidity Constants[a] for Cu(II) Complexes of L^1, L^2, and L^3

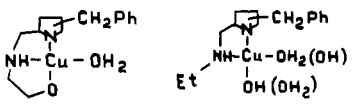
ligand	log K_{CuL}	log K_{CuL_2}	pK'_{a_1}	pK'_{a_2}
L^1	6.72		6.80	10.41
L^2	7.77		7.22	9.36
L^3	10.34	18.0	6.96	9.66

[a] Measured at 30 °C in aqueous 0.1 M $NaNO_3$.

group is substituted by the hydrogen atom in the former compound.

Copper(II) Complexation of the Ligands. In the presence of Cu(II) ions, formation of complexes was indicated by the lower pK_a's of the ligands and by the spectral changes in the solutions. In addition, ionization of copper-bound water molecules and hydroxyalkyl groups was evident in the course of potentiometric titrations. In general, Scheme III describes the type and kind of the equilibriums established at a pH greater than 6.0. The stability constants were refined from potentiometric titration data by using the "Best" program. In the case of each ligand the Cu:L ratios of 1:1 and 1:2 were used for the titrations. No evidence of $Cu(L)_2$ species formation was found for L^1 and L^2, but the compound had to be accounted for in the computation of stability constants for the complex formation between Cu(II) and L^3. The formation constants for the 1:1 complexes of L^3, L^2, and L^1 are presented in Table II and can be seen to lie in the same range as those found earlier for the Cu(II) and 1-benzyl-2-(aminomethyl)pyrrolidine system.[7a] The ionization constants of the coordinated water and hydroxyalkyl groups are also listed there. The species distribution as a function of pH, calculated by using the COMICS program,[8] for L and Cu(II) is plotted in Figure 1.

We believe the first ionization constants for CuL^2 and CuL^3 reflect the hydroxyalkyl group ionization. This is supported by significant changes in the ORD curves, accompanying the titration of these complexes in the pH region 6.2–8.5 (see Figure 2). Coordination of the ionized alkoxy group with the formation of an additional chelate ring in the species **4** could be the underlying



4 **5**

reason for this observation. As expected, no similarity to the case for CuL^2 in the changes of the ORD curves of CuL^1 in the same pH region could be detected, because the corresponding species **5** was derived from the ionization of either of the two coordinated water molecules without any new chelate formation. Finally, the pK_a of *N*-hydroxyethylenediamine in the Cu(II) complex was found to be 7.3,[7b] which was close to the pK_a value determined in this work for CuL_2 (see Table II).

(8) Perrin, D. D.; Sayce, I. J. *Talanta* **1967**, *14*, 833.

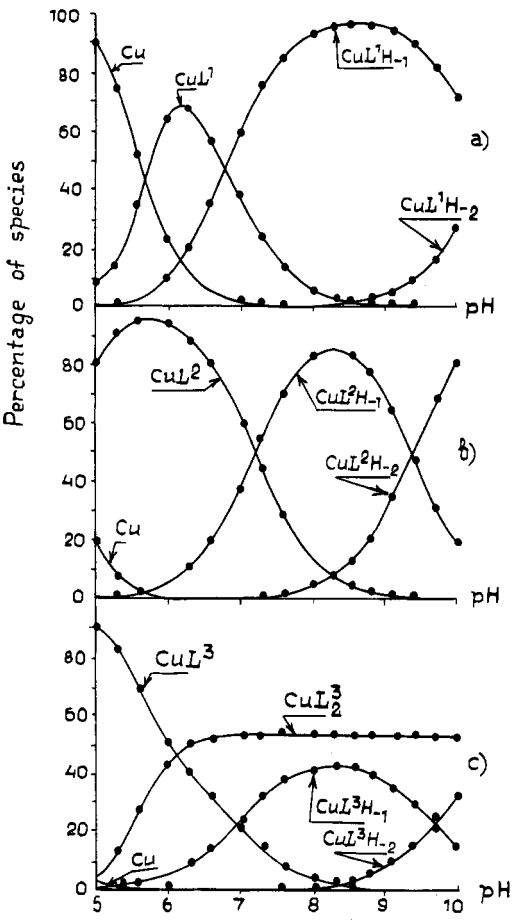


Figure 1. Species distribution as a function of pH plotted with the formation and acidity constants (Table II) for the 1.5:1 L–Cu(II) system: (a) L^1–Cu(II), $[Cu]_T = 7.2 \times 10^{-3}$ M; (b) L^2–Cu(II), $[Cu]_T = 7.1 \times 10^{-3}$ M; (c) L^3–Cu(II), $[Cu]_T = 7.0 \times 10^{-3}$ M.

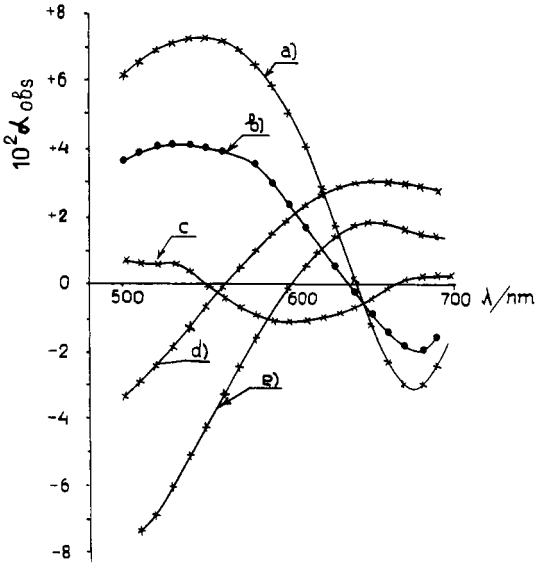


Figure 2. Optical rotatory dispersion curves of CuL^2 (ratio of L^2:Cu(II) = 1:1, $[Cu]_T = 7.7 \times 10^{-3}$ M) in water at 30 °C and pH (a) 6.2, (b) 7.0, (c) 8.5 and of CuL^1 (ratio of L^1:Cu(II) = 1.5:1, $[Cu]_T = 8.0 \times 10^{-3}$ M) in water at 30 °C and pH (d) 6.65 and (e) 8.2.

Additional support for the coordination of the alkoxy group in the CuL^2 (or CuL^3) complex is provided by the X-ray single-crystal analysis data of a dimeric compound obtained from a slowly evaporating CH_3OH solution of equimolar amounts of L^2 (free base), $Cu(NO_3)_2$, and CH_3 ONa.

The dimeric cation (see Figure 3) is formed by the condensation of two molecules with the elimination of H_2O. The copper atoms

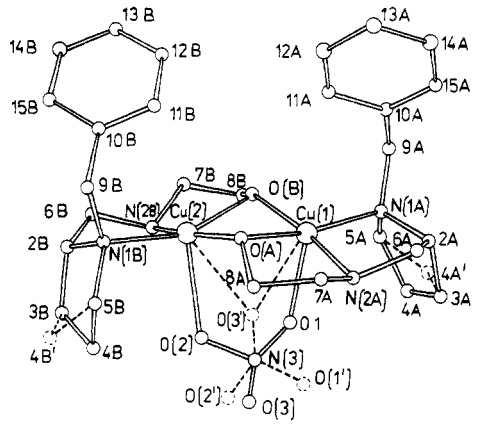


Figure 3. Perspective view of the $[(CuL^2H_{-1})_2(NO_3)]^+$ cation. Alternative positions of disordered atoms are drawn in dashed lines and have primed indexes. H atoms are omitted. Selected bond distances (Å) and angles (deg): Cu(1)–O(A), 1.992 (5); Cu(1)–O(B), 1.915 (5); Cu(1)–N(1A), 2.027 (6); Cu(1)–N(2A), 1.956 (6); Cu(1)–O(1), 2.42 (1); Cu(1)–O(3'), 2.53 (1); Cu(2)–O(A), 1.919 (5); Cu(2)–O(B), 1.966 (5); Cu(2)–N(1B), 2.053 (5); Cu(2)–N(2B), 1.950 (6); Cu(2)–O(2), 2.49 (1); Cu(2)–O(3'), 2.62 (2); Cu(1)···Cu(2), 2.806 (1); Cu(1)–O(A)–Cu(2), 91.7 (2); Cu(1)–O(B)–Cu(2), 92.6 (2).

are bridged by the deprotonated hydroxyethyl groups of L^2 ligands (not unexpectedly for such type of dimerization) and a loosely coordinated axial NO_3 moiety. Although no evidence for the formation of such a dimeric species was found in the water solutions under the hydrolysis experimental conditions, we believe the dimeric structure to be a good model of **4** as far as the mode of the alkoxy group coordination is concerned. Figure 3 shows the crystal structure of the dimer with selected angles and bond lengths. As can be seen from the figure, L^2 serves as a tridentate ligand, leaving one coordination site vacant. There is no doubt that in a dilute aqueous solution the site would be occupied by a water molecule.

Hydrolysis of 2-Cyanopyridine Catalyzed by CuL. Spontaneous hydrolysis of CP under the experimental conditions proceeds very slowly. For example, at pH 8.7 after 48 h 6.3% of CP was consumed, and only 6.3% PAM was the reaction product. Free L did not promote the reaction. However, CP hydrolysis was markedly enhanced in the presence of both L and Cu^{2+} ions.

The hydrolysis was studied in water under pH-stat conditions (pH 6.4–9.4) at 30 °C and a constant ionic strength of 0.1 M. To sustain the solution pH, 0.1 M aqueous NaOH had to be added at pH 9.4, and 0.1 M HCl was used at pH 8.5 and 6.5. The ratio of L:Cu:CP was 1.5:1:1, and the CP concentration was ca. 7×10^{-3} mol L^{-1}. Aliquots of the corresponding reaction mixtures were withdrawn at certain time intervals and adsorbed on and eluted (C_2H_5OH/H_2O, 1:1) from SiO_2. Acidic SiO_2 effectively decomposed the metal complexes present in the solution, and under the experimental conditions only CP, PAM, and PAC were eluted, whereas basic L (L^1, L^2, or L^3), or their basic derivatives, and Cu(II) ions were irreversibly adsorbed on SiO_2. Qualitative and quantitative analyses of CP, PAM, and PAC were conducted with the use the HPLC.

In Figures 4–6 are shown the distributions of products during CP hydrolysis in the presence of Cu^{2+} and L (L^1, Figure 4; L^2, Figure 5; L^3, Figure 6).

Initial rates of CP disappearance in the reaction mixture are presented in Table III. There exists an insignificant dependence of the rates on solution pH (see Table III).

As expected on the basis of similar studies,[9] CP hydrolysis at pH 8.55 and 9.4 in the presence of Cu^{2+} and L^1 yields PAM as the only reaction product (see Figure 4). The amount of CP entering into the reaction is equivalent to that of the PAM formed, or simply, the mass balance is maintained in the course of the hydrolysis.

An additional reaction path is evident in the reaction catalyzed by Cu^{2+} complexes of L^2 and L^3 (see Figures 5 and 6). Besides PAM, PAC is also formed in significant amounts, and its formation follows an induction period where the amount of CP entering into the reaction is not equivalent to the quantity of PAC and PAM formed.

(9) (a) Sakai, K.; Ito, T.; Watanabe, K. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1660. (b) Komiya, S.; Suzuki, S.; Watanabe, K. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1440. (c) Watanabe, K.; Komiya, S.; Suzuki, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2792. (d) Watanabe, K.; Murayama, K. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1948.

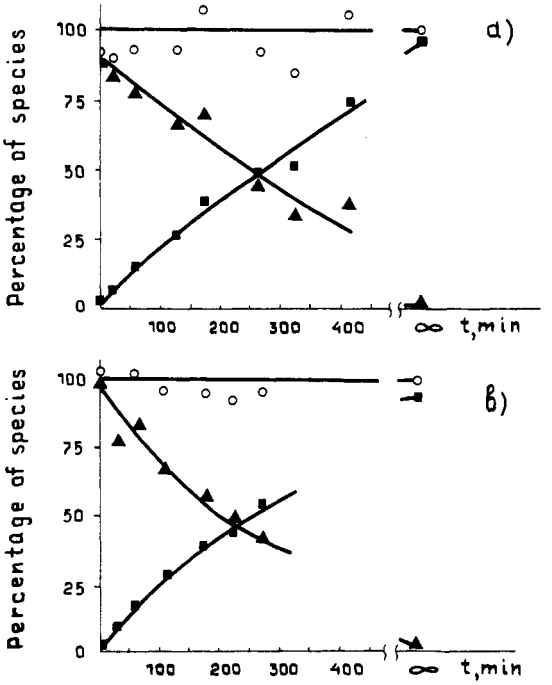


Figure 4. Kinetics of CP disappearance (▲) and PAM formation (■) promoted by the L^1–Cu(II) system in water (30 °C, ratio of CP:Cu:L^1 = 1:1:1.5, $[Cu]_T = 7 \times 10^{-3}$ M) at pH (a) 8.55 and (b) 9.4 and sum of CP and PAM concentrations in the course of the reaction (○).

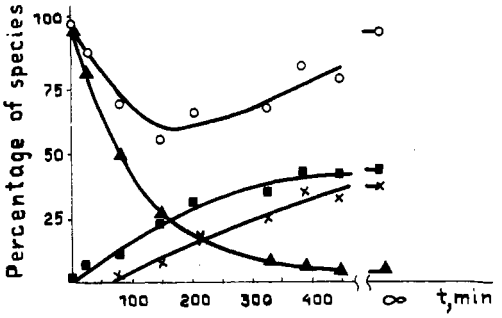


Figure 5. Kinetics of CP disappearance (▲) and formation of PAM (■) and PAC (×) in water (30 °C, ratio of CP:Cu:L^2 = 1:1:1.5, $[Cu]_T = 7 \times 10^{-3}$ M) at pH 8.55 and sum of PAC, CP, and PAM concentrations in the course of the reaction (○).

Table III. Initial Rates of CP Disappearance[a] in Cu(II)-Promoted Hydrolysis in the Presence of L^1, L^2, or L^3

ligand	pH	$10^5 V_0$, M min^{-1}	ligand	pH	$10^5 V_0$, M min^{-1}
L^1	8.55	1.64	L^3	8.55	4.16
L^1	9.4	1.94	L^3	9.4	5.3
L^2	8.55	6.47	spontaneous	8.7	0.019
L^3	6.0	2.32	hydrolysis		

[a] Measured at 30 °C in aqueous 0.1 M $NaNO_3$; L:Cu:CP ratio 1.5:1:1, initial CP concentration ca. 7×10^{-3} M.

Discussion

Large rate enhancements of 10^2–$10^{2.5}$ characterize the CuL^1-, CuL^2-, and CuL^3-catalyzed CP hydrolysis (Table III).

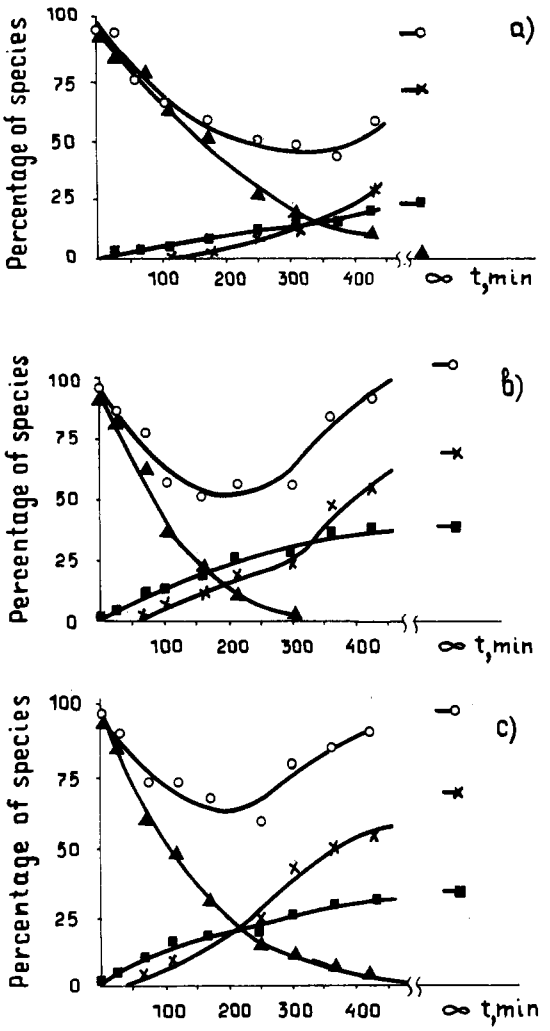
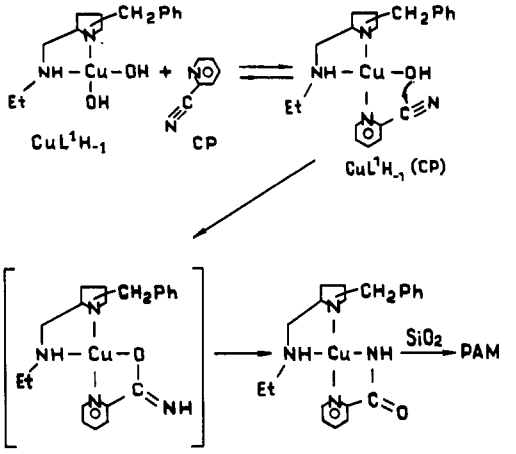


Figure 6. Kinetics of CP disappearance (▲) and formation of PAM (■) and PAC (×) in water (30 °C, ratio of CP:Cu:L^3 = 1:1:1.5, $[Cu]_T = 7 \times 10^{-3}$ M) at pH (a) 6.0, (b) 8.55, and (c) 9.4 and sum of PAC, CP, and PAM concentrations in the course of the reaction (○).

Significant Ni(II), Co(II), and Cu(II) catalysis of CP (or similar substrates) hydration to PAM was observed earlier.[9,10a] It was shown that the substrate structure is important for the catalysis to be actualized. Neither 3- nor 4-cyanopyridine can serve as an effective substrate for the metal ion promoted reaction.[9c] These data are strongly indicative of initial CP coordination to a metal ion, followed by an intra- or intermolecular attack by either the coordinated or the solvent hydroxide ions, respectively (mechanisms B and A).

CP hydrolysis to PAM, catalyzed by CuL^1 according to mechanism B, should proceed through the intermediate species $CuL^1H_{-1}(CP)$ resulting from the interaction of CuL^1H_{-1} and CP (Scheme IV). The rate of the reaction should be proportional to the concentration of this intermediate complex. The kinetic order of CP disappearance depends on the relative magnitude of K (see Scheme V) and the formation constant of a complex between CuL^1 and PAM. If K is large and all CP included in $CuL^1(CP)$, first-order kinetics should be observed. On the other hand, if K is small, and the final product, PAM, exists in solution as $CuL^1(PAM)$, the reaction should follow second-order kinetics. If the formation constants of $CuL^1(CP)$ and $CuL^1(PAM)$ are equal (or close to each other), the reaction ought to follow first-order kinetics under the experimental conditions $[CuL^1]_0:[CP]_0 = 1:1$. Finally, intermediate cases of constant ratios might be expected to result in a mixed kinetic order. Although

Scheme IV



CP disappearance is best described by the first-order kinetics, we made no attempts to discern the equilibrium constants involved in the reaction.

Concentration of $CuL^1(CP)$, in turn, ought to be insignificantly influenced by the solution pH in the pH 8.5–9.4 region, since the concentration of one of the interacting compounds, CuL^1H_{-1}, is almost constant at these pHs (see Figure 3) and the other, CP, is completely deprotonated under the experimental conditions. Moreover, the ratios of CuL^1H_{-1} and $CuL^1H_{-1}(CP)$ in this region should be constant because of the probable similar basicities of these compounds.

In point of fact, $pK_a = 7.2$ for a model Cu(II) complex of 1-[(6-((dimethylamino)methyl)-2-pyridyl)methyl]hexahydro-1,4-diazepin-5-one,[2b] resembling $CuL^1(CP)$, is close to the value found for CuL^1 (see Table II).

Thus, the observed independence of the CP hydrolysis rate on the pH of the solution (see Table III) is a strong argument in favor of the intramolecular hydration of CP in a ternary complex of CP and CuL^1. The ability of coordinated hydroxide to act as a nucleophile in intramolecular hydration of the nitriles coordinated to cobalt(III) was convincingly demonstrated earlier.[2a]

The next, fast step of the reaction is a tautomeric transformation of the intermediate O-coordinated picolinamide to its N-coordinated form. When substituted for a hydrogen, metal ions inhibit the hydrolysis of amide bonds. In particular, it has been established that Cu(II) inhibits hydrolysis of PAM at high pH.[10b] In this way tautomeric transformation effectively blocks further hydrolysis.

Formation of PAM (30–70%) in the CuL^2- and CuL^3-catalyzed hydrolysis of CP (see Figures 5 and 6) can be rationalized by the same mechanism, but formation of 30–70% PAC (see Figures 5 and 6) is an unusual feature that cannot be attributed to hydroxide attack at the CP nitrile group. Since further hydrolysis of PAM to PAC does not occur under the experimental conditions (24 h, 30 °C, pH 8.3) it is the direct conversion of CP to PAC that is brought about by CuL^2 and CuL^3.

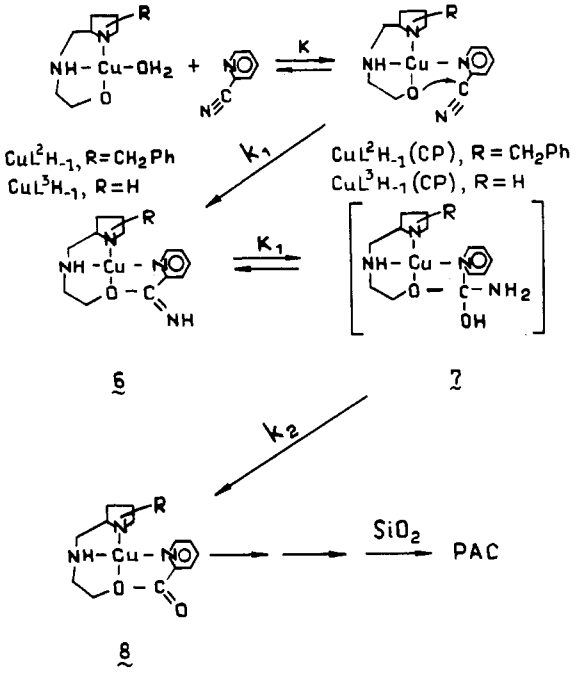
That different transition states are responsible for the formation of PAM and PAC is evident from a significant induction period, after which PAC appeared in the reaction mixture (see Figures 5 and 6).

The only significant difference in the structures of CuL^1, on the one hand, and CuL^2 or CuL^3, on the other, in the pH region 6.5–9.5 is the type of ionized groups in the coordination sphere of the Cu(II) ion. Hydroxide is the only such group in the case of CuL^1H_{-1}, while in the case of CuL^2H_{-1} and CuL^3H_{-1} alkoxy and hydroxide groups are the ligands. It is thus the coordinated ionized hydroxyalkyl group that is responsible for the CP conversion to PAC, catalyzed by CuL^2 and CuL^3.

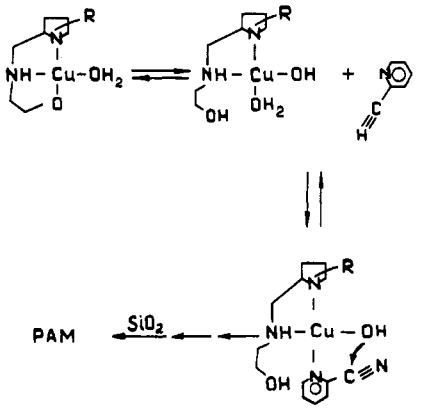
The participation of this group in the process can be rationalized in terms of Scheme V. A rapid equilibrium formation of $CuL^2H_{-1}(CP)$ (or $CuL^3H_{-1}(CP)$) is followed by a slow intramolecular attack of the coordinated alkoxy group on the coordinated CP nitrile group. The stage is irreversible and determines

(10) (a) Breslow, R.; Fairweather, R.; Keana, J. *J. Am. Chem. Soc.* **1967**, *89*, 2153. (b) Conley, H. L.; Martin, R. B. *J. Phys. Chem.* **1965**, *69*, 2914.

Scheme V



Scheme VI



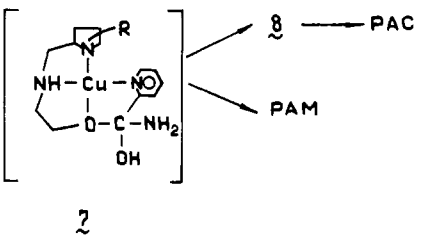
the rate of CP disappearance via the PAC path. A small increase (2-fold) in the initial rates of the reaction catalyzed by CuL^3 in the pH region 6.0–9.4 (see Table III) can be accounted for by the accompanying 3-fold increase in the concentration of the reactive CuL^3H_{-1} species. Only the intermediate coordinated imino ester **6**, by analogy with the hydrolysis of uncoordinated imino esters,[11] can produce any amount of PAC under the hydrolytic conditions.

The coordinated imino ester is stabilized by coordination, and no tautomeric changes of the type presented in Scheme IV become possible.

The buildup of **6** is most probably also responsible for the induction period in PAC formation. This would mean that $Kk_1 > K'k_2$ (Scheme V) or, simply, that the formation of **6** is faster than its hydrolysis to coordinated PAC. Another necessary intermediate, the coordinated ester **8**, should be very reactive because the leaving group (coordinated alkoxy group) has $pK_a = 7.2$, this value being close to that of *p*-nitrophenol. Special experiments showed that PAC *p*-nitrophenyl ester was 80% hydrolyzed within several minutes by CuL^2 and CuL^3 at pH 8.55.

As noted, the accompanying formation of PAM is most likely described by the intramolecular attack of the coordinated hydroxide (Scheme VI). Thus, the difference in the type of CP coordination to CuL^2H_{-1} (or CuL^3H_{-1}) determines whether PAC

Scheme VII



or PAM is the reaction product. If the coordinated water molecule is substituted by CP, the PAC path predominates; in contrast, the substitution of the hydroxyalkyl group leads to PAM formation. Obviously, a greater steric hindrance to H_2O substitution in CuL^3H_{-1} ($R = CH_2C_6H_5$), as compared with CuL^3H_{-1} ($R = H$), can be suggested as explaining the relatively larger proportion of PAM formed in the case of CuL^2H_{-1} (see Figures 5 and 6).

But, if only this mechanism were responsible for PAM formation, one might have expected the ratio of the sum of **6**, **8**, and PAC concentrations to the concentration of PAM to be constant in the course of the process, as is the case for the products of two parallel irreversible reactions of one substrate.[12] The observed ratio changes from 2.4:1 at the beginning of the reaction to 1.4:1 at the end of it for the CuL^2 catalysis and from 3:1 to 2:1 for the catalysis by CuL^3. It is thus possible that some amount of PAM is formed via **7** decomposition, as indicated by Scheme VII.

Conclusions

This paper reports on direct conversion of 2-cyanopyridine to picolinic acid, promoted by Cu(II) complexes, obviating the stage of picolinamide formation. The crucial features of the ligand structure, responsible for the observed reaction path, include the presence of the β-hydroxyethyl group capable of coordination to the metal ion. Intramolecular attack by the coordinated alkoxy group on the nitrile group of coordinated CP is very likely the decisive step of the reaction.

It seems strange that, despite the relatively large number of studies devoted to metal ion promoted amino nitrile hydrolysis,[9] no direct hydrolysis of CP to PAC (or any other type of related conversions) has been reported in the literature. The reason for this can be found in the structure of ligands that are generally employed. Usually those were diamine, polyamine, or carboxylate ligands, and only one paper deals with the hydrolysis of phenanthroline-2-carbonitrile in the presence of Cu(II) ion and *N*-(β-hydroxyethyl)ethylenediamine or ethanolamine as the ligand.[10] However, no phenanthroline-2-carboxylate was found in the reaction mixture. A plausible explanation lies in the weak coordinating ability of ethanolamine, as compared with that of the substrate, a consequence of which was that the ternary complex of two substrate molecules and a Cu(II) ion was the actual reaction species. In the case of *N*-(β-hydroxyethyl)ethylenediamine, a mixed complex may have been formed, where all the coordination sites in the main coordination sphere of the Cu(II) ion are filled by the strong donor ligand atoms with the expulsion of the ligand hydroxyalkyl group.

Finally, our results may have a bearing on the understanding of enzymatic mechanisms. In nature nitriles are hydrolyzed by two different enzymes: nitrile hydratase[13] and nitrilase,[14] which catalyze the conversion of nitriles to amides and acids, respectively. At least one of the enzymes, nitrile hydratase, is a transition-metal-containing enzyme.[15] The structure of the active sites and

(11) Neilson, D. J. In *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; Wiley: New York, 1975; Chapter 9.

(12) Frost, A. A.; Pearson, R. G. *Kinetcs and Mechanism. A Study of Homogeneous Reactions*, 2nd ed.; Wiley: New York, 1962; p 160.

(13) (a) Asono, Y.; Fujishiro, K.; Tani, Y.; Yamada, H. *Agric. Biol. Chem.* **1982**, *46*, 1165. (b) Digeronimo, M. J.; Antoine, A. D. *Appl. Environ. Microbiol.* **1976**, *31*, 900.

(14) (a) Harper, D. B. *Biochem. J.* **1977**, *165*, 309. (b) Hook, R. H.; Robinson, W. G. *J. Biol. Chem.* **1964**, *239*, 4263. (c) Harper, D. B. *Biochem. J.* **1977**, *167*, 685.

(15) Sugiura, Y.; Kuwahara, J.; Nagasawa, T.; Yamada, H. *J. Am. Chem. Soc.* **1987**, *109*, 3848.

the enzyme–substrate intermediates, formed during the hydrolysis of nitriles, are unknown. Clearly, there is a possibility that a hydroxyalkyl side chain of nitrilase protein backbone may serve as a ligand performing the function of a catalytic group directing the hydrolysis toward the acid.

Experimental Section

General Considerations. All the chemicals used were reagent grade. (*S*)-Proline had an optical purity greater than 99%, according to GLC analysis data.[16] 2-Cyanopyridine (Fluka) was used without additional purification. Distilled water was redistilled, boiled, and cooled under an Ar atmosphere to remove any amount of CO_2. Stock NaOH solutions were prepared by dissolving metallic sodium in water under an Ar atmosphere. Stock $Cu(NO_3)_2$ solutions were standardized by complexometric (EDTA) titration, according to established procedures.[17] The ionic strength, $\mu = 0.1$, was adjusted with KNO_3. Measurements of pH and pH-stat titrations were made with the following radiometer apparatus: TTT 1c titrator, SBR 2 titrograph, and ABU 1 autoburet. A constant-temperature bath was used to control the temperature of 30 °C within ±0.1 °C.

^1H NMR spectra were recorded on a Tesla BS 467A spectrometer. Electronic spectra were run on a Specord M-40 instrument. Optical rotation measurements were made with a Perkin-Elmer M241 polarimeter. Rotary dispersion curves were recorded on a Jasco ORD/UV-5 instrument. The stability and acidity constants were computed on a Soviet-made SM-4 minicomputer.

Stability Constants. Stability constants were determined from potentiometric titration data by using the "Best" program[5] kindly provided by the National Research Council of Canada. Free ligands L^1 and L^2 were neutralized with 0.1 M HNO_3 solutions; L^3 was used as its dihydrochloride. Initial $Cu(NO_3)_2$ and ligand concentrations were in the 1.0×10^{-3}–1.0×10^{-4} M range. $pK_w = 13.79$[18] and $pK_a = 8.0$[19] for $Cu(OH_2)_4$ were used in the calculations. The refinements of stability (or acidity) constants were considered satisfactory if the $(pH_{obsd} - pH_{calcd})/pH_{obsd}$ ratio was within the limits of 1% for the buffer regions and 10% for the inflection regions of the potentiometric titration curves. In each case two parallel titrations were made. The calculation results are presented in Tables II and III. Distribution of complex particles under the hydrolysis conditions as a function of pH is plotted in Figure 1. The computation was performed by using the "COMICS" program.[8]

Hydrolysis of CP. The reaction was conducted in a thermostated 20-mL cell under an Ar atmosphere. pHs of solutions were kept constant by adding 0.1 M NaOH or 0.1 M HCl solutions under the pH-stat titration conditions. Initial concentrations of CP were ca. 7×10^{-3} M; the ratio of Cu(II):CP:L was 1:1:1.5. The kinetic runs were initiated by injecting 1 mL of 0.1 M CP solution in CH_3OH into 14 mL of the aqueous solution of an appropriate amount of $Cu(NO_3)_2$ and L, brought to the desired pH. Periodically, a 0.5-mL sample of the solution was withdrawn, put on a SiO_2 column (1 × 3.5 cm), and immediatelyt eluted with a C_2H_5OH/H_2O (1:1) mixture (7 mL).

The eluates were analyzed by using a Perkin-Elmer 601 instrument equipped with an ultraviolet detector operating at 265 nm. Peak areas were determined with a Perkin-Elmer M-2 integrator. Separation of components (CP, PAM, and PAC) was conducted on a 0.46 × 0.25 cm Perkin-Elmer Sil X-I-ODS (10 μm) column under isocratic conditions and 30 °C temperature. The eluant, 10^{-2} M CF_3COOH solution in 10% aqueous MeCN, was charged at a rate 0.75 mL min^{-1}. Sample solutions (50 μm) were introduced into the chromatographic system via a Reodin 702 injector. The components were quantitatively determined with 4-nitrobenzoic acid used as the internal standard. Relative errors of CP, PAM, and PAC determinations were in the range of 3–5%. The experimental results are presented in Figures 4–6.

Preparative Isolation and Characterization of PAC. CP hydrolysis in the presence of Cu(II) and L^3 was conducted in the usual way up to ca. 90% conversion. Cu(II) ions were removed with Dowex A-1 chelating resin buffered with 0.2 M KH_2PO_4. Eluates were combined and evaporated to dryness. The residue was subjected to column chromatography on silica gel (EtOH/concentrated NH_3, 7:4). The fractions containing PAC were collected, evaporated, and dried over P_2O_5. The residue was treated with a mixture of MeCN and *N,O*-bis(trimethylsilyl)trifluoroacetamide (2:1) at 100 °C (0.5 h). The analysis was performed with Kratos MS25RF-DS-55 on a CP Sil 5 CB capillary column (Chromopack). Mass spectrum: *m/e* 195 (M^+, 0.5%), 180 (100), 136 (22.3), 106 (6.2), 80 (46.2).

4-Nitrophenyl picolinate was obtained according to the published method[2c] and had mp 145–146 °C dec (lit.[2c] mp 144–146 °C dec).

(*S*)-*N*-Benzoylproline (1) was synthesized as described earlier and had m.p. 155–157 °C (lit.[9] mp 154–155 °C). Its purity was checked with TLC (SiO_2; acetone/hexane, 1:4).

(*S*)-1-Benzyl-2[(ethylamino)methyl]pyrrolidine (L^1). To a stirred mixture of 6 g (30 mmol) of **1**, 2.46 g (30 mmol) of $EtNH_2$·HCl, and 6.18 g (30 mmol) of dicyclohexylcarbodiimide in 80 mL of dry $CHCl_3$ was added 4.2 mL (10 mmol) of Et_3N. After being stirred for 18 h at room temperature, the solution was consecutively washed with 5% aqueous HCl, H_2O, Na_2CO_3 aqueous solution, and, finally, H_2O. The organic layer was filtered, dried over $MgSO_4$, and evaporated in vacuo. The residue (7.86 g) as an oil with an admixture of crystals was separated on a SiO_2 column (3.5 × 30 cm; $CHCl_3$/acetone, 4:1). A 4.34-g (63.5%) amount of (*S*)-*N*-benzoylproline ethylamide (**2**) as a gummy substance was used without purification. To a mixture of 2.64 g (70 mmol) of $LiAlH_4$ in 20 mL of absolute THF with slow stirring was added a solution of 4.34 g (17.2 mmol) of **2** in 25 mL of THF. After the addition had been completed, the mixture was boiled for another 3.5 h. The reaction mixture was cooled and decomposed with 5.28 mL of 8% aqueous NaOH solution. The precipitate was filtered off, and the filter cake was extracted with boiling THF. The combined THF solution was concentrated under reduced pressure, and the residue was finally distilled in vacuo under N_2. A total of 2.25 g (58.5%) of L^1 was obtained; bp 99–100 °C (3 mmHg). ^1H NMR (DCl in D_2O, DSS internal standard): δ 1.37 (t, 3 H, CH_3), 2.0–2.35 and 2.5–2.7 (m, 4 h, pyrrolidine β,γ-H), 3.18 (t, 2 H, ND_2CH_2–), 3.2–3.6 (m, 2 H, –ND_2CH_2– and pyrrolidine δ-H), 4.0–4.2 (*m*, pyrrolidine α-H), 4.44 and 4.72 (2 H, ND_2CH_2Ar, AB, $J_{AB} = 13$ Hz), 7.6 (br s, 5 H, ArH). Anal. Calcd for $C_{14}H_{22}N_2$: C, 77.02; H, 10.6; N, 12.83. Found: C, 76.91; H, 10.24; N, 12.93. The dihydrochloride of L^1 had mp 216–217 °C.

(*S*)-1-Benzyl-2-[((2-hydroxyethyl)amino)methyl]pyrrolidine (L^2). To a mixture of **1** (10.45 g, 50 mmol) and 6.56 g (50 mmol) of methyl glycinate in 70 mL of absolute $CHCl_3$ was added a solution of dicyclohexylcarbodiimide (10.8 g, 50 mmol) in 70 mL of absolute $CHCl_3$, followed by Et_3N (7.3 mL, 50 mmol) with stirring. The stirring was continued for another 6 h at ambient temperature. The mixture was consecutively washed with 5% aqueous HCl solution, water, an aqueous solution of Na_2CO_3, and water. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel chromatography using a mixture of $CHCl_3$ and acetone (4:1). A total of 9.85 g (71%) of methyl (*S*)-(*N*-benzoylprolyl)glycinate (**3**) was obtained as a gummy substance, which was used without purification. To a suspension of $LiAlH_4$ 4.5 g (12 mmol) in 70 ml of absolute THF was added dropwise a solution of 9.85 g (3 mmol) of **3** in 30 mL of absolute THF with stirring. The reaction mixture was maintained at reflux for 6 h and cooled to 0 °C, and 8% aqueous NaOH solution was added, followed by water, with stirring. The precipitate was filtered off, and the filter cake was extracted with boiling THF. The combined THF solution was concentrated under reduced pressure, and the residue was distilled in vacuo. Ultimately, 5.69 g (72%) of L^2, bp 152–154 °C (3 mmHg), was obtained as a viscous oil. ^1H NMR (D_2O + DCl, DSS internal reference): δ 2.0–2.3 and 2.5–2.7 (m, 4 H, (pyrrolidine β,δ-H), 3.25 (t, 2 H, $-CH_2ND_2$), 3.3–3.6 (m, 4 H, pyrrolidine δ-H and ND_2CH_2–), 3.85 (t, 2 H, $-CH_2O$–), 4.0–4.2 (m, 1 H, pyrrolidine α-H), 4.42 and 4.7 (AB, 2 H, $-CH_2Ar$, $J_{AB} = 13$ Hz), 7.6 (br s, 5 H, ArH). $[\alpha]^{25}$ (λ; nm; *c* 0.87, C_2H_5OH): −41.97 (589), −44.27 (578), −50.46 (546), −87.84 (436), −143.35° (365). Anal. Calcd for $C_{14}H_{22}N_2O$: C, 72.76; H, 9.46; N, 11.95. Found: C, 71.69; H, 9.46; N, 12.50.

(*S*)-2-[((2-Hydroxyethyl)amino)methyl]pyrrolidine (L^3). L_2 (2.89 g, 12.3 mmol) in a mixture of 7.9 mL of CH_3COOH and 25 mL of absolute CH_3OH was hydrogenated over 0.9 g of Pd/Al_2O_3 at ambient temperature and atmospheric pressure. The catalyst was filtered off and washed with CH_3OH. The filtrate and CH_3OH washings were combined and evaporated under reduced pressure. The residue was treated with aqueous 6 M HCl. The mixture was evaporated under reduced pressure; the residue was dried in an evacuated desiccator over P_2O_5. The product was recrystallized from C_2H_5OH. The dihydrochloride of L^3 had mp 136–137 °C. Its ^1H NMR spectrum had ArH signals. $[\alpha]^{25}$ (λ, nm; *c* 1.44, aqueous 6 M HCl): +8.74 (579), +9.15 (578), +10.26 (546), +16.5 (436), +23.99° (365). Anal. Calcd for $C_7H_{16}N_2O \cdot 2HCl$: C, 38.72; H, 8.36; N, 12.90; Cl, 32.66. Found: C, 39.02; H, 8.14; N, 12.93; Cl, 32.50.

X-ray Analysis of $[(CuL^2H_{-2})_2(NO_3)]^+NO_3^-$. The complex crystallizes in the monoclinic space group $P2_1/n$ with $a = 8.532$ (1) Å, $b = 22.803$ (2) Å, $c = 16.408$ (1) Å, $\beta = 97.12$ (1)°, $V = 3167.6$ (4) Å^3, and ρ(calcd) = 1.51 g cm^{-3} for $Z = 4$. (The original L-proline contained a small

(16) (a) Saporovskaya, M. B.; Paskonova, E. A.; Nikitina, S. B.; Vitt, S. V.; Belikov, V. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1974**, *12*, 676. (b) Makaparskin, S.; Birrel, P.; Gil-Av, E.; Oro, Y. *J. Chromatogr. Sci.* **1970**, *8*, 177.
(17) Schwarzenbach, G. *Complexometric Titrations*; Methuen: London, 1957; p 82.
(18) Allison, J. W.; Angelici, R. J. *Inorg. Chem.* **1971**, *10*, 2233.
(19) Gustafson, R. L.; Martell, A. E. *J. Am. Chem. Soc.* **1959**, *81*, 525.

admixture of the D form. Racemic crystals were thus isolated, probably due to a lower solubility of the centrosymmetric substance.) Intensity data were collected by using a Hilger & Watts diffractometer (Mo Kα radiation, θ-2θ scan technique, $2\theta \leq 56°$, 3533 observed reflections with $I \geq 2\sigma(I)$). The structure was solved by Patterson and difference Fourier syntheses. The O(1), O(2), O(3), C(4A), and C(4B) atoms (see Figure 3) appeared disordered by two positions each, which were refined independently with a fixed occupancy factor of 0.5. The positional and anisotropic thermal parameters of all non-hydrogen atoms were refined (including H atoms as fixed contributions in calculated positions) to $R_f = 0.059$ and $R_{wF} = 0.065$.

Registry No. **1**, 5874-58-8; **2**, 116279-38-0; **6** (R = $PhCH_2$), 116324-20-0; CP, 100-70-9; (*S*)-L^1, 116279-36-8; (*S*)-L^1·2HCl, 116279-39-1; (*S*)-L^2, 113443-54-2; (*S*)-L^3, 116279-37-9; (*S*)-L^3·2HCl, 116279-40-4; CuL^1, 116324-25-5; CuL^2, 116324-24-4; CuL^3, 116324-23-3; $[(CuL^2H_{-1})_2(NO_3)]^+NO_3^-$, 116324-22-2; picolinamide, 1452-77-3; picolinic acid, 98-98-6; 4-nitrophenyl picolinate, 74104-89-5; methyl glycinate, 616-34-2; methyl (*S*)-(*N*-benzoylprolyl)glycinate, 113443-55-3.

Supplementary Material Available: Tables of atomic coordinates, all bond distances and angles, and thermal parameters (5 pages). Ordering information is given on any current masthead page.

Contribution from the Institute for Inorganic Chemistry, University of Witten/Herdecke, Stockumer Strasse 10, 5810 Witten, Federal Republic of Germany

Kinetics and Mechanism of the Ligand Substitution Reactions of Ethylenediaminetetraacetate Complexes of Ruthenium(III) in Aqueous Solution

H. C. Bajaj[1] and R. van Eldik*

Received April 26, 1988

The kinetics of the substitution reactions of $Ru(edta)H_2O^-$ with SCN^-, N_3^-, thiourea, and substituted thiourea were studied as a function of pH (2-9), temperature (20-45 °C) and pressure (0.1-100 MPa). The activation parameters at pH 5 fall in the ranges $22 \leq \Delta H^{\ddagger} \leq 37$ kJ mol^{-1}, $-105 \leq \Delta S^{\ddagger} \leq -99$ J K^{-1} mol^{-1}, and $-12 \leq \Delta V^{\ddagger} \leq -7$ cm^3 mol^{-1} and support the operation of an associative ligand substitution mechanism. The results are discussed in terms of the extraordinary lability of the $Ru(edta)H_2O^-$ species, and arguments are presented in favor of an I_a mechanism.

Introduction

Our general interest in the substitution behavior of transition-metal edta (ethylenediaminetetraacetate) complexes was stimulated by reports on the catalytic activity of such complexes, especially those of Fe(II) and Fe(III), in the simultaneous removal of NO_x and SO_2 from flue gases of coal-fired power plants.[2-4] Furthermore, the edta ligand is generally used to remove traces of free metal ions that may, for instance, catalyze oxidation processes.[5] In such cases it is usually accepted that this ligand blocks off all of the coordination sites. However, many studies in recent years have shown that this is not necessarily the case, since edta can coordinate with between one and six donor atoms to the metal center, leaving the remaining coordination sites free for eventual catalytic activity.[6]

Preliminary studies on the substitution reactions of Fe^{III}(edta) in our laboratories revealed that many of these reactions are either too fast for conventional stopped-flow measurements or exhibit almost no UV-vis spectral changes.[7] In order to gain more insight into the fundamental nature of such substitution processes, we first studied the substitution behavior of the corresponding Ru(III) complex. This complex is significantly less reactive than the corresponding Fe(III) species, and the substitution reactions are accompanied by significant spectral changes. Furthermore, when Ru(III) is bound to edta, its lability is increased to such an extent (by at least 7 orders of magnitude) that it undergoes substitution more rapidly than Ru(II).[8] The edta complex of Ru(III) has been shown to be pentadentate in aqueous solution, for which the sixth coordination site of the metal center is occupied by a water molecule at low pH or by a hydroxide ion at high pH.[9] The complex exhibits two characteristic pK_a values, which are associated with the following equilibria:[10,11]

$$Ru(Hedta)H_2O \overset{K_1}{\rightleftharpoons} Ru(edta)H_2O^- + H^+ \quad pK_1 = 2.4 \qquad (1)$$

$$Ru(edta)H_2O^- \overset{K_2}{\rightleftharpoons} Ru(edta)OH^{2-} + H^+ \quad pK_2 = 7.6 \qquad (2)$$

Kinetics studies[9,12,13] on the substitution (anation) behavior of these complexes clearly indicate a maximum reactivity at $4 < pH < 6$, where the observed rate constant is practically independent of pH. This was ascribed to the extreme lability of $Ru(edta)H_2O^-$ for which the specific ligand geometry enables an associative substitution mode.[9] However, the reason for this high lability is still unsettled in the literature.[6] In contrast, the corresponding reactions of the Ru(II) analogue are significantly slower and suggested to proceed according to a dissociative mechanism.[9,14,15]

In an effort to contribute toward the understanding of the high lability of Ru(III)-edta complexes, we have undertaken a systematic study of the substitution behavior of this complex with a series of nucleophiles. Some uncharged nucleophiles were selected in order to minimize electrostriction effects that may affect the interpretation of the activation parameters, especially the entropy and volume of activation.[16]

Experimental Section

Materials. $K[Ru(Hedta)Cl]\cdot 2H_2O$ was prepared from $K_2[RuCl_5(H_2O)]$ as described in the literature.[14,17] This complex was charac-

* Author to whom correspondence should be addressed.

(1) On leave from the Central Salt and Marine Chemicals Research Institute, Gijubhai Badheka Marg., Bhavnagar 364002, India.
(2) Schrod, M.; Semel, J.; Steiner, R. *Chem.-Ing.-Tech.* **1985**, *57*, 717.
(3) Chang, S.-G., Littlejohn, D.; Lynn, S. *Environ. Sci. Technol.* **1983**, *17*, 649.
(4) Sada, E.; Kumazawa, H.; Hikosaka, H. *Ind. Eng. Chem Fundam.* **1986**, *25*, 386.
(5) van Eldik, R. In *Chemistry of Multiphase Atmospheric System*; Jaeschke, W., Ed.; Springer-Verlag: West Berlin, 1986; p 541.
(6) Ogino, H.; Shimura, M. *Adv. Inorg. Bioinorg. Mech.* **1986**, *4*, 107.
(7) Bajaj, H. C.; Braun, P.; Dellert, M.; van Eldik, R., unpublished results.
(8) Matsubara, T.; Creutz, C. *J. Am. Chem. Soc.* **1978**, *100*, 6255.
(9) Matsubara, T.; Creutz, C. *Inorg. Chem.* **1979**, *18*, 1956.
(10) Mukaida, M.; Okuno, H.; Ishimori, T. *Nippon Kagaku Zasshi* **1965**, *86*, 589.
(11) Shimizu, K.; Matsubara, T.; Sato, G. P. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1651.
(12) Yoshino, Y.; Uehiro, T.; Saito, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1060.
(13) Toma, H. E.; Santos, P. S.; Mattioli, M. P. D.; Oliveira, L. A. A. *Polyhedron*, **1987**, *6*, 603.
(14) Diamantis, A. A.; Dubrawski, J. V. *Inorg. Chem.* **1981**, *20*, 1142.
(15) Ojo, J. F.; Olubuyide, O.; Oyetunji, O. *J. Chem. Soc., Dalton Trans.* **1987**, 957.
(16) van Eldik, R., Ed. *Inorganic High Pressure Chemistry: Kinetics and Mechanisms*; Elsevier: Amsterdam, 1986.

0020-1669/88/1327-4052$01.50/0