ance of IIa for the two extraction solvents are in excellent agreement.

Dehydrofluorination of IIIa. A sample (60% IIIa, 40% IIa) containing approximately 1 mg of IIIa dissolved in diglyme was added to an aqueous diglyme mixture maintained at 50°, resulting in 12 ml of a 30% aqueous diglyme solution which was approximately 6×10^{-4} *M* IIIa. At 0 and 100% reaction, 5.0-ml aliquots were withdrawn and extracted with 0.7 ml of benzene. The aqueous extracts were analyzed for developing hydrofluoric acid content by titration with standard sodium hydroxide solution; the organic extracts were analyzed directly by vpc for organic product. Only production of one organic product, the most abundant geometric isomer, IIb, was observed. The concentration of IIc was too low to be detected. The amount of the impurity, IIa, did not increase during the course of the reaction.

Dehydrofluorination of IIIb. When the diglyme sample (91% IIIb, 9% IIa) containing approximately 3 mg of IIIb was added to an aqueous diglyme mixture maintained at 50°, 20 ml of a 30% aqueous diglyme solution, which was approximately 1.1×10^{-3} *M* IIIb, was obtained. After 0, ~75, and 100% reaction, 5.0-ml aliquots were withdrawn and extracted with 0.7 ml of benzene. Again the aqueous phase was titrated with standard sodium hydroxide solution for developing acidity, and the organic phase was analyzed by vpc for organic product. The only observable products were hydrofluoric acid and the two geometric isomers, IIa and IIb. The total yield of organic product was at least 90%. The final ratio of IIa to IIb, corrected for the initial amount of IIa, was 24.2 (±6%) to 1. The integrated rate constant for decomposition of IIIb was 2.96×10^{-4} sec^{-1}; this value was actually used for k_3. The measured value for production of IIa from IIIb was 3.42×10^{-4} sec^{-1}, while the corresponding rate constant for hydrogen ion production was 2.4×10^{-4} sec^{-1}. When 73% of IIIb had disappeared, 78% of IIa and from 64 to 67% of the hydrogen ion had appeared. These percentages, and consequently the rate constants, are in very good agreement, considering the accuracy of the determinations for the small sample employed.

Acknowledgment. The authors are indebted to Mr. Derek Tegg for assistance in the handling and isolation of the compounds and to Professor John I. Brauman for many helpful discussions.

Metal-Catalyzed Hydration of Phenanthroline Nitrile[1]

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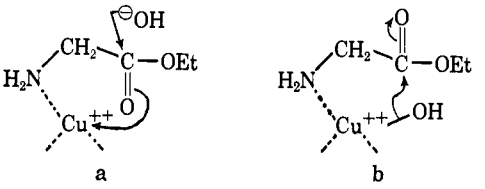
Abstract: The hydration of 2-cyano-1,10-phenanthroline to the corresponding amide is strongly promoted by metal ions such as Cu^{2+}, Ni^{2+}, and Zn^{2+}; with Ni^{2+}, the reaction is first order in metal–substrate complex and first order in hydroxide ion. The second-order rate constant for the Ni^{2+}-catalyzed process is 10^7 that for the alkaline hydration in the absence of metal; the entire acceleration is accounted for by the change in $\Delta S^{\ddagger}$. With Cu^{2+}, the acceleration by metal is of the order of 10^9. Studies with nucleophiles other than hydroxide ion show that the mechanism of metal-catalyzed addition to the nitrile probably involves external attack, with the metal acting as a general acid, rather than the kinetically equivalent attack by nucleophile from the metal coordination sphere. The hydrolysis of the product amide to the carboxylic acid shows much weaker metal catalysis. The contrast between these two hydrolysis reactions is perhaps related to the "rack" mechanism which has been proposed for some enzymatic processes.

The metal-catalyzed hydrolysis of coordinating substrates is a subject of continued interest.[4] Such processes represent attractive models for the catalytic role of metals in some enzymatic hydrolyses,[5] but they also pose interesting mechanistic problems. For instance, the well-known[6] hydrolysis of glycine ethyl ester, catalyzed by Cu^{2+}, is first order in metal, substrate, and hydroxide ion.[7] Two kinetically equivalent mechanisms can be considered for such a process: (a) attack by external hydroxide ion with the metal serving to stabilize the developing carbonyl anion, or (b) attack on the carbonyl group by metal-bound hydroxide ion.

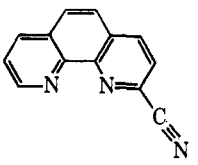


The two processes cannot be distinguished by simple kinetic tests (their transition states differ only in the position of one proton). Busch has shown[8] that when an intermediate related to mechanism a is prepared, using Co^{3+}, it will hydrolyze according to mechanism a; however, as he points out, this does not show that mechanism a is in fact followed except in this special case.

For a variety of reasons we decided to study the metal-catalyzed reactions of 2-cyano-1,10-phenanthroline (I). This substrate has the advantage that it should be strongly and completely bound to various metal ions, and that the cyano group is in a well-defined position within a metal complex, near the metal, but for reasons

(1) Support of this work by the National Institutes of Health is gratefully acknowledged.
(2) National Institutes of Health Predoctoral Fellow, 1964–1967.
(3) National Science Foundation Postdoctoral Fellow, 1964–1965.
(4) *Cf.*, M. L. Bender, "Reactions of Coordinated Ligands," Advances in Chemistry Series, No. 37, American Chemical Society, Washington, D. C., 1963, Chapter 2.
(5) For a review of metal-activated enzymes, see B. L. Vallee, "The Enzymes," 2nd ed, P. D. Boyer, H. Lardy, and K. Myrbäck, Ed., Academic Press Inc., New York, N. Y., 1960, Chapter 5.
(6) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1889 (1957).
(7) D. Chipman, Ph.D. Thesis, Columbia University, 1965.
(8) M. D. Alexander and D. H. Busch, *J. Am. Chem. Soc.*, **88**, 1130 (1966).

of geometry not coordinated with it. We were particularly interested in the distinction between mechanisms a and b, since with the latter it should be possible to promote addition to the nitrile of other ligands on the metal. Such ligand–ligand reactions are of interest as enzyme models,[9] and as we will discuss below they can be used to help distinguish between mechanisms a and b in metal-promoted processes.



I

Experimental Section

Materials. 2-Cyano-1,10-phenanthroline (I) was prepared from 1,10-phenanthroline by the method of Corey.[10] The crude material was purified by three recrystallizations from acetonitrile, mp 238–239° (lit.[10] mp 237–238°).

1,10-Phenanthroline-2-carbonamide (II). A solution of 20.5 mg (0.100 mmole) of 2-cyano-1,10-phenanthroline, mp 238–240°, in 15 ml of water containing 0.200 mmole of hydrochloric acid and 0.100 mmole of cupric chloride was titrated with 0.5 *N* sodium hydroxide solution until the pH of the final solution was 10. The color of the initial solution was light blue-green; the final solution was a deeper blue. Upon treatment of the final solution with 0.200 mmole of EDTA disodium salt, the amide (II) separated from the solution as a white crystalline solid, 24 mg (*ca.* 100% yield). Two recrystallizations from ethanol afforded the analytical specimen as white needles, mp 304.5–305.5°.

Anal. Calcd for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 70.27; H, 4.20; N, 18.86.

The expected parent ion peak at *m/e* 223 was observed in the mass spectrum of the substance. The substance demonstrated pronounced infrared absorption (KBr) at 3400, 1685, 1660, 1485, 1385, and 872 cm^{-1}. The ultraviolet spectrum showed λ_{max}^{water} 278 mμ (ε 30,500) and 232 mμ (ε 42,000).

Kinetic Measurements. Kinetic measurements of the Ni^{2+}-catalyzed hydration of I were performed on a Cary Model 11 spectrophotometer using the following method. Into a jacketed, 10-cm cell were pipetted 5 ml each of 0.2 *M* $NiCl_2$, 0.2 *M* 2,6-lutidine buffer, and 0.7 *M* NaCl solutions, and the volume was adjusted to 33.0 ml with distilled water. The cell was fitted into the spectrophotometer and water circulated through the cell jacket from an external constant-temperature bath maintainable to within 0.05°. After allowing at least 20 min for temperature equilibration, 200 μl of a 0.025 *M* acetonitrile solution of I was injected. Mixing was accomplished by inverting and shaking the cell at least three times. The disappearance of absorbance at 344.0 mμ was followed for at least four half-lives. The pH of the solution was measured on a Radiometer TTTlc titrimeter in another jacketed cell at the temperature of the reaction.

Kinetic measurements of the base-catalyzed hydration of I were performed on a Cary Model 15 spectrophotometer using the following procedure. A solution of 1.0 *N* NaOH (2.5 ml) was placed in a 1-cm cuvette; the cuvette was stoppered and placed in a thermostated cell holder within the cell compartment of the spectrophotometer. Water was circulated through the cell holder from an external constant-temperature bath maintainable to within 0.1°. After 20 min for temperature equilibration, 55 μl of 2.5×10^{-3} *M* solution of I in acetonitrile was injected, the cuvette stoppered, and the contents mixed by inverting several times. The disappearance of absorbance at the isosbestic point, as determined below (275.2–275.7 mμ), was followed.

Determination of Isosbestic Point. The determination of the isosbestic point of the hydrolysis of 1,10-phenanthroline-2-carbonamide to the corresponding carboxylate was performed on a Cary Model 15 spectrophotometer with a repetitive scan attachment. A solution of 1.0 *N* NaOH (2.5 ml) was placed in a 1-cm cuvette and the cuvette stoppered and placed in the thermostated cell holder as described above. 1,10-Phenanthroline-2-carbonamide hydrochloride (50 μl, 1.0×10^{-3} *M*) was injected, and the region from 300 to 230 mμ repetitively scanned as a function of time. The maximum at 276 mμ shifted to 273 mμ with an isosbestic point at 275.2 mμ (at 45.0°). At 25.0° the isosbestic point occurred at 275.7 mμ.

Isolation Experiments and Product Analysis. A typical mixed-complex experiment is conducted as follows. The required amount of the second ligand was dissolved in 5 ml of water, 1 ml of 0.1 *M* $CuCl_2$ solution was added, and the pH of this solution was adjusted to the operating pH of the reaction. In a separate vessel, 20.5 mg (0.1 mmole) of I was dissolved in 5 ml of redistilled THF by gentle warming, and, after cooling to room temperature, the two solutions were mixed, the volume made up to 22 ml, and the pH adjusted to the operating value.

The reaction was quenched by adding an excess of EDTA solution, adjusting the pH to 10.0, and extracting the aqueous phase with chloroform. The chloroform extracts were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was weighed to determine the amount of material recovered.

Infrared analysis of the solid residues was conducted by making a 2% (by weight) mixture of KBr, shaking the mixture on a "Wigglebug" for 30 sec, and making 70 mg into a pellet by a standard procedure. Quantitative estimates of I and II were made by comparison of the absorptions at 845 and 872 cm^{-1}, respectively, with known standards.

Thin layer chromatography analyses of residues were carried out on microslides coated with silica gel G. Mixtures of acetone and methanol were used as eluting agents, and all cases were run against known compounds.

Results

The pK_a of 2-cyano-1,10-phenanthroline is 3.82 ± 0.02 (25°, 0.1 *M* KCl), the electron-withdrawing effect of the nitrile group lowering the basicity by more than one pH unit compared with the unsubstituted 1,10-phenanthroline, whose pK_a is 5.00 under the same conditions.[11] The nitrile forms an emerald colored complex with copper sulfate, but addition of EDTA disodium salt to this solution results in the quantitative isolation of the corresponding amide II. This cupric-catalyzed hydration reaction is extremely rapid; at 25° and pH 6–7, attempted kinetic measurements place the half-life at less than 10 sec. The reaction is effectively blocked by addition of 1 equiv of phenanthroline. The hydration is also catalyzed by Ni^{2+} and Zn^{2+}, the rate, however, being slower than in the Cu^{2+}-catalyzed case. In all of these cases the only isolable product is the corresponding amide II.

The Ni^{2+}-catalyzed hydration was chosen for kinetic study since the reaction has a moderate half-life and is convenient to follow spectroscopically. The association constant for the Ni^{2+} complex of I is $(3 \pm 1) \times 10^3$ M^{-1}, and the Ni^{2+} concentration is kept large enough to ensure that all of the nitrile is complexed. In the region pH 5.05–7.15 at 30.0°, the Ni^{2+}-catalyzed hydration is first order in hydroxide ion, following the equation: $k_{obsd} = k_2(OH^-)^\alpha$ with $\alpha = (0.991 \pm 0.011)$ and $k_2 = (1.6 \pm 0.8) \times 10^6$ M^{-1} min^{-1} (see Table I). In addition the rate is independent of the concentration of 2,6-lutidine buffer. Determination of the activation parameters from the data of Table II yields the values: $\Delta H^\ddagger = (15.7 \pm 0.2)$ kcal/mole, and $\Delta S^\ddagger = +(14 \pm 1)$ eu. The activation parameters for the sodium hydroxide catalyzed hydration reaction are: $\Delta H^\ddagger = (15.1 \pm 1.2)$ kcal/mole, and $\Delta S^\ddagger = -(20 \pm 4)$ eu (see Table III). That the sodium hydroxide reaction is

(9) R. Breslow and D. Chipman, *J. Am. Chem. Soc.*, 87, 4195 (1965), and subsequent unpublished work.

(10) E. J. Corey, A. L. Borror, and T. Foglia, *J. Org. Chem.*, 30, 288 (1965).

(11) C. V. Banks and R. C. Bystroff, *J. Am. Chem. Soc.*, 81, 6153 (1959).

not catalyzed by Na^+, complexing with the substrate is demonstrated by the fact that when the reaction is run using the same concentration of tetramethylammonium hydroxide, the rate constants are identical within experimental error.

Table I. Ni^{2+}-Catalyzed Hydration of 2-Cyano-1,10-phenanthroline (I) (pH Dependence)[a]

pH	k_{obsd}, min^{-1}
5.05	$(3.31 \pm 0.02) \times 10^{-3}$
5.67	$(1.31 \pm 0.01) \times 10^{-2}$
5.97	$(2.46 \pm 0.02) \times 10^{-2}$
6.25	$(4.48 \pm 0.04) \times 10^{-2}$
6.46	$(7.40 \pm 0.05) \times 10^{-2}$
6.85	$(1.90 \pm 0.01) \times 10^{-1}$
7.15	$(3.91 \pm 0.04) \times 10^{-1}$

[a] 30.0°, $NiSO_4 = 6.0 \times 10^{-2}$ *M*, substrate = 1.5×10^{-4} *M*, buffer = 3.0×10^{-2} *M*. A plot of log (k_{obsd}) *vs.* pH using a least-squares computer program yields a straight line of slope = (0.991 ± 0.011) (correlation coefficient = 0.99943) and intercept = −(7.51 ± 0.07).

Table II. Ni^{2+}-Catalyzed Hydration of 2-Cyano-1,10-phenanthroline (I) (Temperature Dependence)[a]

Temp, °C	pH[b]	$a_{OH^-} \times 10^{-8}$ *M*[c]	k_{obsd}, min^{-1}	k_2, M^{-1} min^{-1}[d]
25	6.51	3.26	4.72×10^{-2}	1.45×10^6
25	6.51	3.26	4.63×10^{-2}	1.42×10^6
30	6.39	3.61	8.21×10^{-2}	2.28×10^6
30	6.39	3.61	7.91×10^{-2}	2.19×10^6
40	6.14	4.03	2.15×10^{-1}	5.33×10^6
40	6.14	4.03	2.08×10^{-1}	5.17×10^6
45	6.02	4.20	3.31×10^{-1}	7.88×10^6
45	6.02	4.20	3.46×10^{-1}	8.24×10^6

[a] $NiCl_2 = 3.0 \times 10^{-2}$ *M*, substrate = 1.5×10^{-4} *M*, buffer = 3.0×10^{-2} *M*, 0.105 *M* NaCl. [b] pH measured at temperature of reaction. [c] Calculated for $a_{OH^-} = K_w/a_{H^+}$. [d] Calculated from $k_2 = k_{obsd}/a_{OH^-}$.

Table III. Alkaline Hydration of 2-Cyano-1,10-phenanthroline to the Amide (II) (Temperature Dependence)[a]

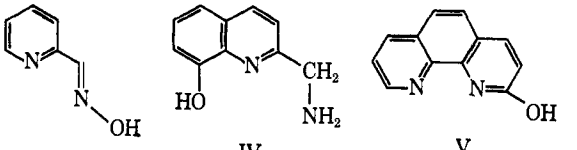
Temp, °C	k_2, M^{-1} min^{-1}[b]
25.0	0.154
35.0	0.325
45.0	0.811

[a] 1.0 *M* NaOH. [b] $k_2 = k_{obsd}$, since $(OH^-) = 1$ *M*.

In the sodium hydroxide hydration, the amide II is hydrolyzed further to carboxylate at a rate $^1/_{15}$ that of the hydration of I. However, in the Ni^{2+}-promoted hydration of I no subsequent hydrolysis is observed. A kinetic study of the hydrolysis of the Ni^{2+} monocomplex of II under our standard conditions at pH 7.60 and 50.0° gives $k_{obsd} = 7.3 \times 10^{-5}$ min^{-1} ($t_{1/2}$ = 158 hr) and thus $k_2^{50°} = 3.3 \times 10^1$ min^{-1} M^{-1}. For hydration of the Ni^{2+} monocomplex of I, extrapolation of the data in Table II give $k_2^{50°} = 1.2 \times 10^7$ min^{-1} M^{-1}. Thus Ni^{2+} (as a 1:1 complex) promotes the hydration of I to II by a factor of 10^7, but promotes the hydrolysis of II to the carboxylate salt by only 4×10^2.

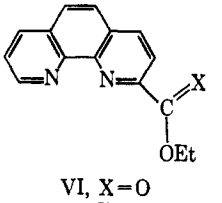
In an effort to determine if I would react with a second chelate bearing a nucleophilic group, equimolar amounts of I, metal, and second chelate were combined and allowed to react at room temperature for various lengths of time, the metal was sequestered by addition of EDTA, and the organic products were extracted and analyzed.

Although we have found[9] that metal complexes of 2-pyridinecarboxaldoxime (III) act as good intracomplex nucleophiles with some bound substrates, reaction of I with the Ni^{2+} or Zn^{2+} monocomplexes of III under a variety of conditions leads only to II. Similarly,



III IV V

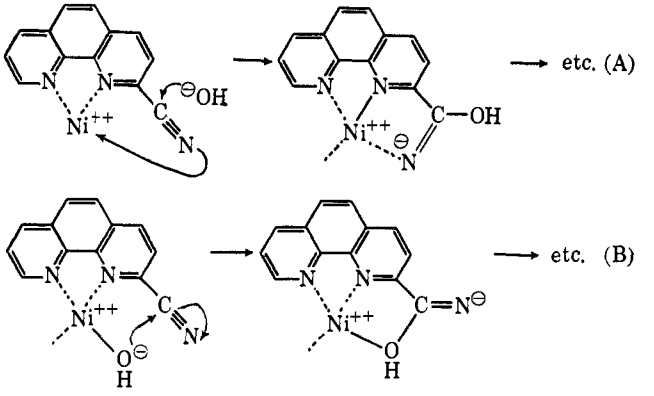
reaction of I with the Zn^{2+} or Cu^{2+} monocomplexes of IV, or the Cu^{2+} monocomplex of V, lead only to II. With varying amounts of ethylenediamine, the Cu^{2+}-promoted conversion of I to II could be slowed, but no other product was detectable. With high concentrations of ethanolamine, at pH 9, some attack of ethanolamine on I could be detected, but the proportion was the same in the presence or absence of Cu^{2+}. With 1 equiv of hydroxyethylethylenediamine, at pH's 9, 10, and 11 where it is fully bound, I and Cu^{2+} gave only II. When I was dissolved in 50 mole % water–ethanol at pH 6.7 with 1 equiv of Ni^{2+} and allowed to stand for 20 min, followed by quenching with sodium EDTA solution and mild acid work-up, the product was 85% of phenanthrolinecarboxylic acid ethyl ester (VI), identical with an authentic sample, 10% of the amide II, and 5% of the imino ester VII.



VI, X=O
VII, X=NH

Discussion

The fact that the Ni^{2+}-catalyzed hydration of I is first order in hydroxide and is not susceptible to general basic catalysis is consistent with either of two general mechanisms: (A) attack of external hydroxide on the complexed substrate, or (B) attack of a coordinated hydroxide on the complexed substrate.



Both mechanisms account for all the simple observations on this reaction, but mechanism B implies attack on the ligand by a second group coordinated with the

metal, and this was looked for. No second ligand could be made to replace hydroxide ion in the addition reaction. Especially striking is the observation that coordinated alcohols, such as ethanolamine and hydroxyethylethylenediamine, are no more nucleophilic in the metal-catalyzed addition to I than in the metal-free control. Such alcohols should be present in high concentration in the metal coodination sphere, and thus by mechanism B they should have shown enhanced reactivities. The experiment in 50% aqueous ethanol shows that ethanol is more reactive than water, as generally is observed[12] for simple nucleophilicities. This in itself makes mechanism B unlikely, since coordination of ethanol to the metal (in the transition state for the reaction) is very unfavorable[13] relative to coordination of water, so the normal nucleophilic ratio should not have been observed. The normal reactivity of ethanol also makes even more striking the unreactivity of strongly coordinated alcohols according to mechanism B. However, all these facts are completely consistent with mechanism A, and we adopt it as correct.

If one compares the activation parameters for the Ni^{2+}-catalyzed and the alkaline-catalyzed reactions of I, it is apparent that the difference in rate of the two reactions, a factor of 10^7 at 25°, is due totally to the difference in the entropies of activation of the two processes. The values of $\Delta H^{\ddagger} = 15.1$ kcal/mole and $\Delta S^{\ddagger} = -20$ eu for the base-catalyzed reaction are reasonably consistent with other values reported for hydroxide-catalyzed nitrile hydrolysis.[14,15] For example, Wiberg[15] finds $\Delta H^{\ddagger} = 21.2$ kcal/mole and $\Delta S^{\ddagger} = -12$ eu for the alkaline hydrolysis of benzonitrile in 50% aqueous acetone. On the other hand, the unusually large positive entropy of activation ($\Delta S^{\ddagger} = +14$ eu) in the Ni^{2+}-catalyzed case seems inconsistent with what is usually expected for a bimolecular process.[16] For mechanism A to be consistent with this observation, the transition state must involve bonding of the developing imino anion to the metal ion, perhaps displacing a coordinated water molecule at the adjacent site, but in any case requiring less solvation (and liberating the solvent shell around the nucleophile).

The hydroperoxide anion addition to benzonitrile[15] has $\Delta H^{\ddagger} = (22 \pm 1)$ kcal/mole, and $\Delta S^{\ddagger} = +(5 \pm 4)$ eu. Here again is a bimolecular process with a positive entropy of activation, which one can interpret as involving less solvent restriction through a cyclic transition state in which the proton on oxygen helps to "solvate" the developing negative charge on nitrogen.

It is of considerable interest that the coordinated metal also can catalyze[17] the hydrolysis of the amide II. Because of the rigidity of II it seems clear that only a mechanism of type A would be permitted in this case, since from spectroscopic evidence the carboxamido group is certainly coordinated with the metal and independent coordination of a hydroxide ion between the metal and the amide group seems sterically forbidden. However, with Ni^{2+}, the catalysis (ratio of second-order rate constants for the complexed and free substrate) is only four hundred-fold, compared with the ten million-fold acceleration of the hydration of I. This probably reflects the fact that the cyano group in I is not coordinated with metal, and indeed probably prevents normal coordination of a water molecule by sterically blocking the metal ligand site. Thus, coordination is gained in the transition state for hydration. By contrast, in the hydrolysis of II both the starting state and the transition state are coordinated. This phenomenon is intellectually related to the "rack mechanism" which has been postulated[18] for some enzymatic processes, according to which binding of the substrate to an enzyme induces a distortion toward the geometry of the transition state. In any case, it clearly shows that stronger metal catalysis can be observed for a group which is not initially in a perfect position for metal coordination.

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(13) R. F. Pasternack, *Dissertation Abstr.*, 24, 503 (1963).
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(15) K. Wiberg, *J. Am. Chem. Soc.*, 77, 2520 (1955).
(16) For a review, see L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, 1, 1 (1963).
(17) E. Gabbay, in unpublished work, has also studied the Zn^{2+}-promoted hydrolysis of 2-carbethoxy-1,10-phenanthroline.
(18) H. Eyring, R. Lumry, and J. D. Spikes in "The Mechanism of Enzyme Action," W. D. McElroy and B. Glass, Ed., Johns Hopkins Press, Baltimore, Md., 1954, p 123.