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Studies on Girard Hydrazone. IV.[1] Effect of Cupric Ion on the Hydrolysis of Girard Hydrazone

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It has been found that cupric ion retards the rates of hydrolysis of Girard T hydrazones formed from aliphatic carbonyl compounds. The reduced rates approach to the magnitude expected for the rate-determining hydronium ion catalyzed decomposition of the intermediate amino-alcohols. Cupric ion has almost no effect of the hydrolysis of the Girard T hydrazone of acetophenone or the Girard D hydrazone of acetone. The results are interpreted in terms of an inhibition of hydrolysis through the dipolar form of amino-alcohol intermediate by cupric ion.

In the previous paper kinetic studies of the hydrolysis of Girard hydrazone in aqueous solution were reported and the mechanism of hydrolysis was discussed.[1] Thus in the hydrolysis of Girard hydrazone derived from aliphatic carbonyl compounds, a change in the rate-determining step from the rate-determining decomposition of the intermediate amino-alcohol in the highly acidic region to a rate-determining attack of water (or hydroxide ion) on the substrate in slightly acidic, neutral, and alkaline regions, was demonstrated. In the case of aromatic Girard hydrazones, on the other hand, only acid catalyzed rate-determining decomposition of intermediate was observed in the pH region studied. This paper is on the effect of metal ions on the hydrolysis. It has been found that the rates of hydrolysis of Girard T hydrazones prepared from aliphatic carbonyl compounds were retarded in the presence of cupric ions. The role of cupric ion in the hydrolysis is discussed in this paper.

Experimental

Materials——Girard T reagent (Merck, G.R.) was recrystallized from absolute ethanol. Girard D reagent, prepared by a known method,[3] was recrystallized from ethanol. Girard hydrazones were prepared as described previously.[1,4] *p*-Chlorobenzylidene-1,1-dimethylethylamine[5] and benzylidenemethylamine[6] were prepared by known methods. The metal salts were of reagent grade and were used without further purification. Compounds used for buffer solution were also of reagent grade. Other organic reagents, such as semicarbazide hydrochloride, were recrystallized from appropriate solvents.

Apparatus——Polarographic measurements were made with a Yokogawa type POL-11 polarograph. Spectrophotometric measurements were made with a Shimazu, type QV-50, spectrophotometer and a Hitachi, type EPS-3T, recording spectrophotometer. A Tōadempa, model HM-5A, pH meter with glass-saturated calomel electrode was used for pH measurements. pH titration of Girard reagent–cupric ion system was carried out as described previously.[7]

Visible Spectra——Visible spectra of Girard hydrazones in the presence of cupric ion were obtained by extrapolation to zero time, because of their noticeable hydrolysis.

A definite amount of 0.1N NaOH solution ($f=1.006$) and suitable amount of water were put into a 10 ml volumetric flask. A volume of 0.50 ml of ethanolic solution of a Girard hydrazone, 1.00 ml of 0.1M cupric sulfate solution, and the necessary amount of water to make up the correct volume were added to the flask in the order. The mixture was shaken quickly and the visible spectra were obtained for several time intervals. The resulting mixture contained 0.02M of the Girard hydrazone. The pH of the mixture

1) Part III: M. Masui and H. Ohmori, *J. Chem. Soc.* (*B*), 1967, 762.
2) Location: *Toneyama 6-5, Toyonaka, Osaka-fu.*
3) M. Viscontini and J. Meier, *Helv. Chim. Acta*, **33**, 1773 (1950).
4) M. Masui and H. Ohmori, *Chem. Pharm. Bull.* (Tokyo), **12**, 877 (1964).
5) E.H. Cordes and W.P. Jencks, *J. Am. Chem. Soc.*, **85**, 2843 (1963).
6) K. Kindler, *Ann. Chem.*, **431**, 226 (1923).

was also measured at the same time. Time zero was taken at the point where half of the pipetting solution of Girard hydrazone was added.

Kinetic Measurement——Reactions were followed polarographically at 25±0.05° as described previously.[1] In the presence of transition metal ions, measurements were made spectrophotometrically, because the large polarographic reduction wave of the metal ions disturbed the reduction wave of Girard hydrazones. In the absence of these metal ions, the rates of hydrolysis obtained by the spectrophotometric method coincided with those obtained by polarographic method within the limits of experimental error (less than 4%). Generally the spectrophotometric method was carried out as follows. A volume of 23 or 48 ml of buffer solution, with the desired amount of metal salt, if required, was put into a 25 or 50 ml volumetric flask and warmed to 25±0.05° in a thermo-controlled water bath. A volume of 0.50 or 1.00 ml of ethanolic solution of a Girard hydrazone and the necessary amount of buffer solution to make up the correct volume, both at 25°, were added to the flask. The resulting mixture was shaken quickly, and then stood in the bath. The resulting mixture contained 5×10^{-4}M of the Girard hydrazone. At appropriate intervals 1.00 ml of the solution was pipetted into 9.00 ml of water and the absorbance due to unreacted Girard hydrazone was measured. A correction was made by extrapolation for the time lapse from mixing with water to reading of absorbance. The rate constant for the reaction was obtained graphically using the usual pseudo-first order kinetic treatment.

Buffer Solutions——The buffer systems used in the absence of heavy metal ions were the same as those described previously.[1] When a transition metal ion was added, 0.01—0.05M acetate buffer was used and rates were obtained mainly at pH 3—5. Rates were not obtained at above pH 7, because metal hydroxides precipitated in alkaline media. The ionic strength was maintained at 0.5 by the addition of KCl unless otherwise specified.

Product Analysis——Acetone Girard T hydrazone (1.04×10^{-3}M) was hydrolyzed at pH 4.50 (0.04M acetate buffer) and 25°. 25.0 ml of the reaction mixture was pipetted, and 5.0 ml of water and 30.0 ml of 0.1M acetate buffer (pH 5.00) containing excess (>0.02M) isobutyraldehyde were added. After adding 0.60 ml of 1% gelatin solution as a maximum suppressor, the polarogram due to isobutyraldehyde Girard T hydrazone was recorded by the usual method. Under the condition the formation of isobutyraldehyde Girard T hydrazone was completed within 5 minutes. The height of the reduction wave ($E_{1/2}=-1.17$ V *vs.* SCE) was 3.37 μA and this showed that the concentration of the hydrazone in the test solution was 4.03×10^{-4}M. Hence the recovered concentration of Girard T reagent in the original reaction mixture was 0.967×10^{-3}M. The calibration curve for isobutyaldehyde Girard T hydrazone was prepared by the same method using weighed sample of free Girard T reagent.

In the presence of cupric ions Girard T reagent itself was rather unstable, that is, 1.0×10^{-3}M of the reagent was decomposed almost completely within 30 minutes at 25° in 0.04M acetate buffer (pH 4.50) containing 0.02M cupric ion. Hence Girard T reagent could not be recovered quantitatively from the reaction mixture containing cupric ions if the duration of the hydrolysis reaction was long. But the following observations would support the view that the hydrolysis of Girard T hydrazone was normal even in the presence of cupric ions.

a) Aceton Girard T hydrazone (1.00×10^{-3}M) was hydrolyzed for 2 hr[8] at 25° in 0.04M acetate buffer (pH 4.50) containing 0.02M cupric ion and excess (>0.02M) isobutyraldehyde. To 25.0 ml of the reaction mixture 5.0 ml of 0.2M oxalic acid was added to precipitate cupric ion. To 10.0 ml of the filtrate 10.0 ml of 0.1M acetate buffer (pH 5.00) containing excess (>0.02M) isobutyraldehyde and 0.20 ml of 1% gelatine solution were added. From the polarogram of the solution, the concentration of isobutyraldehyde Girard T hydrazone was determined to be 4.07×10^{-4}M, from which the concentration of Girard T reagent in the original reaction mixture was calculated to be 0.977×10^{-3}M.

b) The effect of isobutyraldehyde on the rate of hydrolysis of acetone Girard T hydrazone was found to be negligible. The experiment in the absence of cupric ion is as follows. When 1.00×10^{-3}M acetone Girard T hydrazone was hydrolyzed in 0.04M acetate buffer (pH 4.50) containing excess (>0.02M) isobutyraldehyde, the rate of formation of isobutylaldehyde Girard T hydrazone, measured polarographically,[9] was in good agreement with the rate of hydrolysis of acetone Girard T hydrazone in the same solution without isobutyraldehyde. In the presence of cupric ions, though the effect of isobutyraldehyde could not be examined, because the high concentration of cupric ion disturbed the polarographic test, and the spectrophotometric method could not identify the above two hydrazones, it may highly probable that isobutyraldehyde has negligible effect on the hydrolysis.

c) The Girard hydrazone itself is stable in the presence of cupric ions if the hydrolysis does not take place, as this was found in dry methanol solution.

7) M. Masui and H. Ohmori, *J. Chem. Soc.* (*A*), **1969**, 153.
8) When the hydrolysis was carried out without isobutyraldehyde 93% of the hydrazone was hydrolyzed in the time (this was found from the rate measurement by spectrophotometric method).
9) The polarographic wave of isobutyraldehyde Girard T hydrazone is distinguishable from that of acetone Girard T hydrazone.

Result

Cupric ion retards the rates of hydrolysis of the Girard T hydrazones of acetone, phenylacetone, and cyclopentanone, which are aliphatic carbonyl compounds, as shown in Fig. 1.

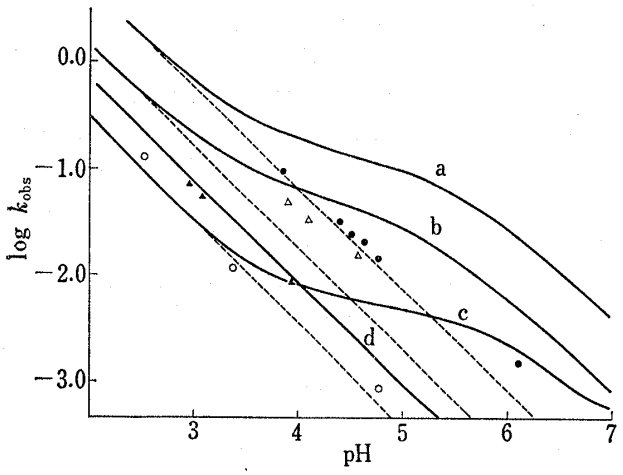


Fig. 1. pH-Rate Profiles of Hydrolysis of Girard T Hydrazones in the Presence and Absence (solid lines)[a] of Cupric Ions

k_{obs} : Observed pseudo-first order rate constant.
a: acetone Girard T hydrazone (•),[b] b: phenylacetone Girard T hydrazone (△), c: cyclopentanone Girard T hydrazone (○), d: acetophenone Girard T hydrazone (▲)

a) Rates represented by solid lines, which were obtained by extrapolation to zero buffer concentration, are quoted from previous papers (ref. 1 and M. Masui and H. Ohmori, *J. Chem. Soc.*, 3951, (1964)) except for that of acetone Girard T hydroazone. The rate of hydrolysis of each Girard T hydrazone was measured at various pH values both by polarographic and spectrophotometric methods to substantiate the reproducibility of the results.

b) The rates represented by solid circles, open circles, etc., were obtained from runs carried out in 0.01—0.03M acetate or phosphate buffer in the presence of 0.01—0.03M cupric ion.

All rates were measured at 25° and μ=0.5 with KCl.

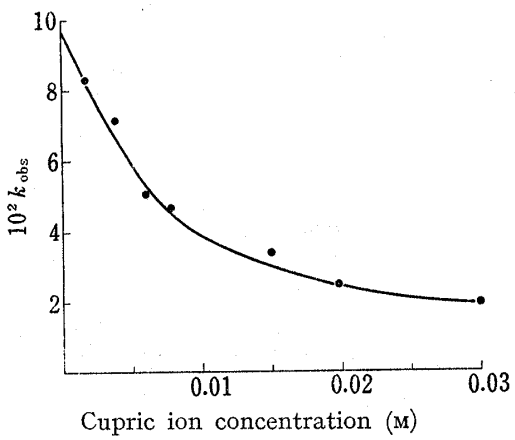


Fig. 2. Effect of Cupric Ion Concentration on the Hydrolysis of Acetone Girard T Hydrazone at pH 4.64 (0.05 M acetate buffer) and 25°

μ=0.5 with KCl; the initial concentration of acetone Girard T hydrazone was 5×10^{-4}M.

On the other hand, cupric ion has no effect on the hydrolysis of the Girard T hydrazone of acetophenone which is an aromatic carbonyl compound. Several other metal ions tested (Ni^{2+}, Co^{2+}, Pb^{2+}, Fe^{2+}, Fe^{3+}, Mn^{2+}, and Al^{3+}) had no effect, even on the hydrolysis of the Girard T hydrazones of acetone, phenylacetone, and cyclopentanone. Under the experimental conditions used cupric ion was found to have no effect on the hydrolysis of some other azomethine compounds, such as acetone semicarbazone, *p*-chlorobenzylidene-1,1-dimethylethylamine, and benzylidenemethylamine. At a fixed pH value, the rate-retarding effect of cupric ion on the hydrolysis of acetone Girard T hydrazone approaches a limiting value when the cupric ion concentration is more than 0.02M, as shown in Fig. 2. The rate did not decrease below that expected for the rate-determining hydronium ion catalyzed decomposition of the intermediate amino-alcohols (Fig. 1 broken lines).

The visible spectra of Girard hydrazone-cupric ion mixture (Fig. 3 and 4) are closely related to those of Girard reagent-cupric ion system,[7] which indicate that similar complexes are formed in these systems. The change of pH of Girard hydrazone–cupric ion mixture with the addition of alkali (Fig. 5) also support this view, because similar proton dissociation was observed in the case of Girard reagent–cupric ion system.[7]

The change in absorbance at 242 mμ with time of acetone Girard D hydrazone at pH 4.65 in the presence of cupric ion is shown in Fig. 6, and at the end of the run, the reaction mixture showed an absorption maximum at 237 mμ (εc=0.46, the concentration of ligand was 1×10^{-4}M). In the absence of cupric ion, the solution of acetone Girard D hydrazone had essentially no absorption band at the end of a run. In acetone Girard T hydrazone, no band such as that

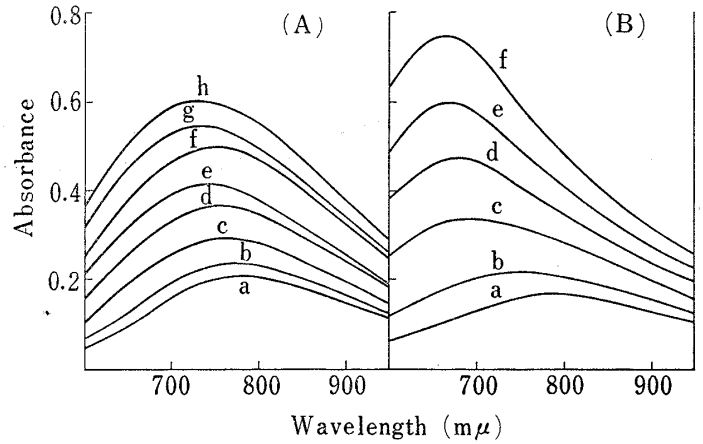


Fig. 3. Absorption Spectra of Girard T Hydrazone (0.02 M)-Cupric Ion(0.01 M) Mixtures in Aqueous Solution (Light Path 1 cm)

(A) acetone Girard T hydrazone at pH (a) 3.46, (b) 3.70, (c) 4.15, (d) 4.29, (e) 4.65, (f) 4.89, (g) 5.52, and (h) 6.80
(B) acetophenone Girard T hydrazone at pH (a) 3.71, (b) 4.21, (c) 4.57, (d) 4.86, (e) 5.09, and (f) 5.41

was observed even in the presence of cupric ion. An absorption band similar to that was obtained with a mixture of Girard D reagent and cupric ion when the concentrations of reagents and the experimental conditions were the same as for the run of acetone Girard D hydrazone. The rate of the initial decrease in absorbance seen in Fig. 6 coincides with the rate of hydrolysis of acetone Girard D hydrazone at the same pH, in the absence of cupric ion. These results suggest that cupric ion has no effect on the hydrolysis of acetone Girard D hydrazone unlike acetone Girard T hydrazone.

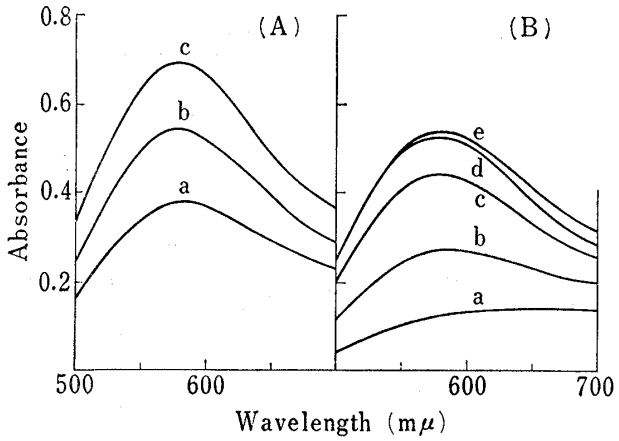


Fig. 4. Absorption Spectra of Girard D Hydrazone (0.02 M)-Cupric Ion(0.01 M) Mixture in Aqueous Solution (light path 0.5 cm)

(A) acetone Girard D hydrazone at pH (a) 3.20, (b) 3.51, and (c) 10.07
(B) isobutylaldehyde Girard D hydrazone at pH (a) 3.41, (b) 3.57, (c) 4.15, (d) 6.60, and (e) 7.63

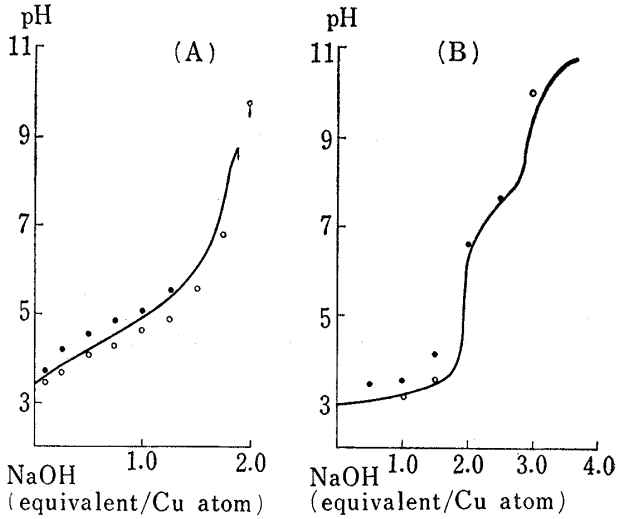


Fig. 5. Titration Curves of Girard Reagents (0.02M) in the Presence of Cupric Ions(0.01 M), and Change of pH of Girard Hydrazone (0.02 M)–Cupric Ion(0.01 M) Mixture with the Addition of Sodium Hydroxide

(A) solid line, Girard T reagent; open cirlce, acetone Girard T hydrazone; solid circle, acetophenone Girard T hydrazone
(B) solid line, Girard D reagent; open circle, acetone Girard D hydrazone; solid circle, isobutyraldehyde Girard D hydrazone

Discussion

The hydrolysis of Girard hydrazone is reported as a two step reaction (Chart 1) similar to that of other azomethine compounds, as previously reported,[1] and the observed pseudo-first order rate constant, k_{obs}, becomes as represented in Eq. 1.

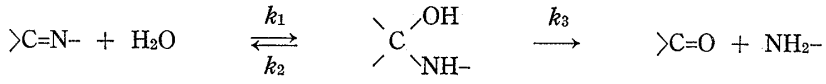


Chart 1

$$k_{obs}=k_1k_2/(k_2+k_3) \qquad \text{Eq. 1}$$

Where k_1, k_2, and k_3 represent the apparent rate constants containing a catalytic and a non-catalytic term in each step. From the results in Fig. 3 and 5 together with a study on formation of a complex between Girard T reagent and cupric ion,[7] it might seem reasonable first to consider a participation of cupric ion as shown in Chart 2.

If cupric ion mainly effects the k_1 step, the observed rate retardation should be due to the higher stability of complex I in Chart 2. Since a complex such as II might also exist,[10] in such case, and the formation of a complex such as III has already been confirmed,[7] the reaction should proceed by a path, I⇄II→III. However, an acceleration rather than retardation of hydrolsyis is generally expected from a reaction path such as this, and several examples, such as super-acid catalysis of metal ions, have been reported.[11]

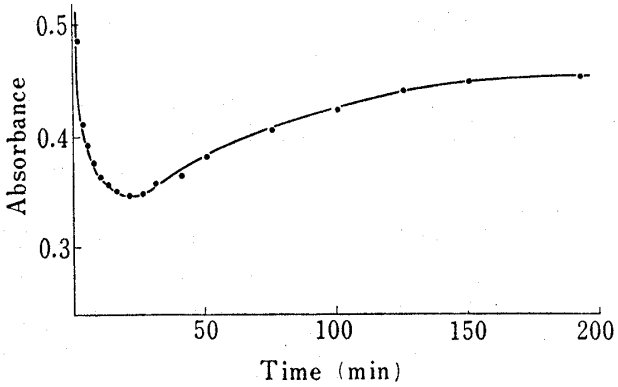


Fig. 6. Change in Absorbance at 242 mμ with Time on Hydrolysis of Acetone Girard D Hydrazone (1.0×10^{-3}M) in the Presence of Cupric Ion (0.01M) at pH 4.65 (0.02M acetate buffer) and 25°.
μ=0.5 with KCl

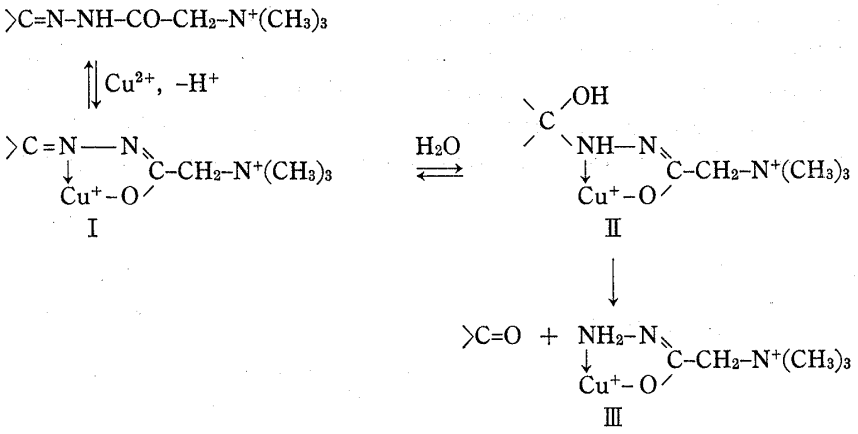


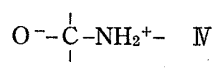
Chart 2

On the other hand, the hydrolysis of glycylglycine in basic media has been found to be completely inhibited by formation of a complex of substrate with cupric ion.[12] In this case, a proton is dissociated from the peptide nitrogen atom and the double bond character between the carbonyl carbon and the peptide nitrogen increases. This reduces the possibility of formation of a tetrahedral addition intermediate, and this is the main factor responsible for the effect on the rate. A similar effect of cupric ion was also reported in weakly acid media.[13] In Girard

10) D.L. Leussing and C.K. Stanfield, *J. Am. Chem. Soc.*, **88**, 5726 (1966); M.E. Fargo and T. Matteus, *J. Chem. Soc. (A)*, 1969, 609.
11) *a*) G.L. Eichhorn and J.C. Bailar, Jr., *J. Am. Chem. Soc.*, **75**, 2905 (1953); G.L. Eichhorn and I.M. Trachtenberg, *ibid.*, **76**, 5183, (1954); G.L. Eichhorn and N.D. Marchand, *ibid.*, **78**, 2688 (1956); *b*) H. Kroll, *J. Am. Chem. Soc.*, **74**, 2036 (1952); L. Meriwether and F.H. Westheimer, *ibid.*, **78**, 5119 (1956); J.B. Longenecker and E.E. Snell, *ibid.*, **79**, 142 (1957); M.L. Bender and B.W. Turnquest, *ibid.*, **79**, 1889 (1957); M.D. Alexander and D.H. Bush, *ibid.*, **88**, 1130 (1966); *c*) H.L. Conley, Jr. and R.B. Martin, *J. Phys. Chem.*, **69**, 2914, 2923 (1965).
12) M.M. Jones, T.J. Cook, and S. Brammer, *J. Inorg. Nucl. Chem.*, **28**, 1265 (1966).
13) I.J. Grant and R.W. Hay, *Aust. J. Chem.*, **18**, 1189 (1965).

T hydrazones, however, because the reaction center is different from that in the above compounds though there is a similar proton dissociation and increased double bond character between the carbonyl carbon and the amide nitrogen, the effect of cupric ion is believed to be different. The proton dissociation results in an increase in the negative charge on the reactant, but this is mostly compensated for by the positive charge on the cupric ion. In view of the charge effect, an enhancement of rate can be expected, because there is one net positive charge increase, as suggested by Hay and Morris.[14] Moreover, even if the stabilization of Girard T hydrazone by formation of a complex such as I occurs, it should be difficult to explain by this alone why the rates are not retarded less than those represented by the broken lines in Fig. 1.

If cupric ion inhibits the k_3 step, the participation of a complex as II must be considered first. In this case, however, an increase in rate is to be expected, as described above. It has been reported that cupric ion inhibits the hydrolysis of glycinamide, when coordination takes place at the amide nitrogen, whereas acceleration is observed when coordination occurs at the carbonyl oxygen.[11c] Coordination at the amide nitrogen involves the reaction site in the chelate ring, whereas coordination at the carbonyl oxygen leaves the reaction site outside the chelate ring, and the observed effect is in agreement with the suggestion of Eichhorn, *et al.*[11a] In the case of Girard T hydrazone, the reaction site is outside the chelate ring.



IV

Thus, although the mechanism of the effect of cupric ion is still not quite clear, the following explanation may be possible. It has been suggested that in the hydrolysis of an azomethine compound a strongly basic amine is only expelled from a dipolar intermediate such as IV.[5,15] In the hydrolysis of Girard hydrazones, decomposition of the intermediate amino-alcohol proceeds through both the acid-catalyzed and non-catalyzed term.[1] If this non-catalyzed term is due to the dipolar form, a participation of cupric ion as shown in Chart 3 may be possible.

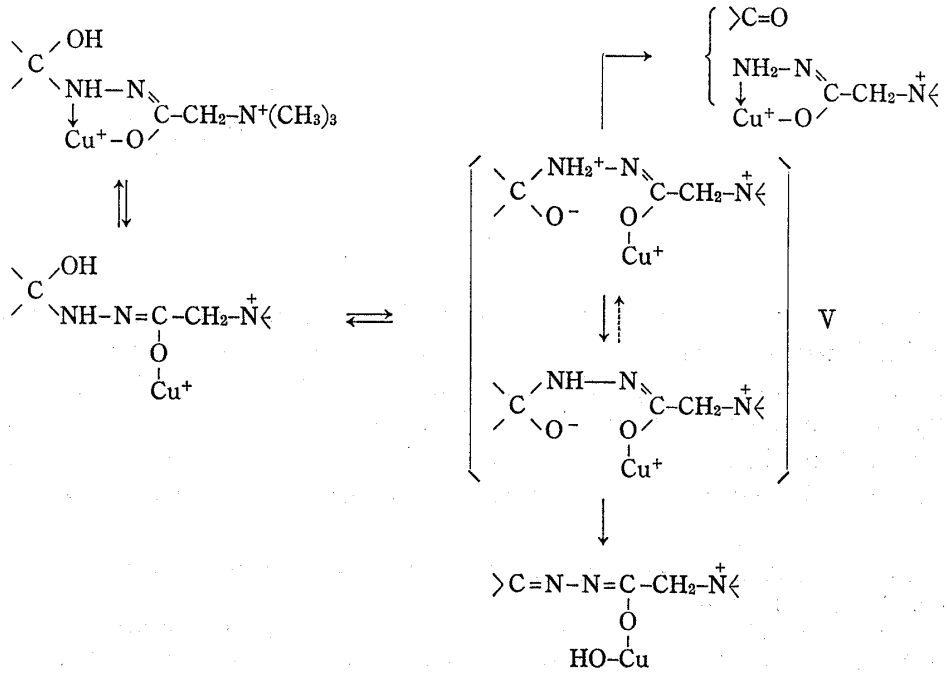


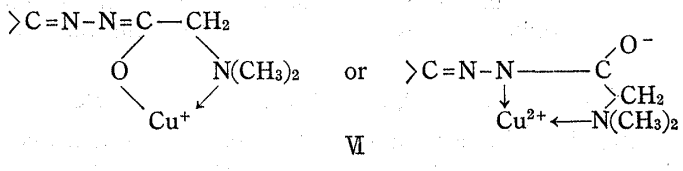
Chart 3

14) R.W. Hay and P.J. Morris, *Chem. Commun.*, **1967**, 23.
15) K. Koehler, W. Sandstrom, and E.H. Cordes, *J. Am. Chem. Soc.*, **86**, 2413 (1964); G.L. Schmir and B.A. Cunningham, *ibid.*, **87**, 5692 (1965).

Thus cupric ion may inhibited the formation of the dipolar intermediate (V), k_3, or catalyze the dehydration of V to the hydrazone, k_2, and inhibit the non-catalyzed decomposition of the amino-alcohol to the final products. Hence the rate of hydrolysis should decrease to the value expected for the hydronium ion catalyzed decomposition of the amino-alcohol (Fig. 1 broken lines). Since in the hydrolysis of acetophenone Girard T hydrazone the non-catalyzed decomposition of intermediate amino-alcohol did not occur in the pH region studied,[1] no rate-retarding effect of cupric ion is observed.

The interpretation for the difference between the hydrolysis rate of Girard T and D hydrazone reported previously,[1] is interesting in this connection. In this case, the intramolecular contribution of the terminal dimethylammonium group to the azomethine nitrogen, which seemed plausible becuase of the geometrical structure, did not operate in Girard D hydrazone, but another intramolecular general acid catalysis for the dehydration of the intermediate amino-alcohol to the hydrazone was consistent with the results obtained.

The mechanism of hydrolysis of acetone Girard D hydrazone was found to be almost the same as that of acetone Girard T hydrazone.[1] In the presence of cupric ions, however, the behaviour of acetone Girard D hydrazone is quite different from that of acetone Girard T hydrazone. This differnce may be associated with the fact that Girard D reagent forms a different type of complex from Girard T reagent with cupric ion.[7] Thus in the case of acetone Girard D hydrazone, cupric ion preferentially coordinates to the terminal tertiary nitrogen atom (VI), which prevents the cupric ion from interacting with the reaction center. Although a proton dissociation occurs at the hydrazide nitrogen atom as well as at terminal nitrogen atom, no rate-retarding effect, such as that in the hydrolysis of Girard T hydrazone, was detected. This result is consistent with the view that the rate effect observed in the hydrolysis of Girard T hydrazone is not attributable to proton dissociation only. A direct interaction of cupric ion with the reaction site is necessary for cupric ion to exert an inhibitory action on the hydrolysis of Girard hydrazones.



VI