

Hydrolysis of 5-Chloro-7-iodo-8-quinolinol Conjugates catalyzed by Metal Ions

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Glucuronide (CF-G) and sulfate (CF-S) of 5-chloro-7-iodo-8-quinolinol were hydrolyzed in water in the presence of metal ions at pH 7. In this condition, CF-G was hydrolyzed more easily than CF-S. The rate of the hydrolysis, pseudo-first order reaction, was in parallel with the stability constants of 8-quinolinol-metal complexes. The rate of hydrolysis increased with reduction of concentration of H⁺ and tris buffer suppressed the hydrolysis of CF-G. These results suggest that metal catalyzed hydrolysis of CF-G and CF-S was derived from the formation of complexes between the conjugates and metal ions.

During the study on the metabolism of 5-chloro-7-iodo-8-quinolinol (chinfoform; CF), it was found that CF glucuronide (CF-G) and sulfate (CF-S) were hydrolyzed in a rat body.²⁾

On the other hand, some investigators had reported the metal-ion catalyzed hydrolysis of glucosides³⁾ and sulfates⁴⁾ of 8-quinolinol, and CF-S.⁵⁾

In this work, the hydrolysis of CF-G and CF-S was examined in the aqueous solution containing Cu²⁺, Ni²⁺, Zn²⁺, Mg²⁺, and Ca²⁺.

Materials and Instruments

CF-G and CF-S used were synthesized according to Matsunaga's and Chen's methods. All nitrates of metal ions, Cu(NO₃)₂, Ni(NO₃)₂, Zn(NO₃)₂, Mg(NO₃)₂, and Ca(NO₃)₂, and tris-(hydroxymethyl)aminomethane (tris) were reagent grade. Phenolphthalein mono-glucuronide was purchased from Chugai Pharmaceutical Co. Determination of CF-G and CF-S was performed with Du-Pont 830 Liquid Chromatograph.⁶⁾

Solutions for reaction were prepared as follows: CF-G, CF-S or phenolphthalein mono-glucuronide was dissolved in dist. water in concentration of 1 × 10⁻³M. Each nitrate of metal ions was dissolved in dist. water in concentration of 1 × 10⁻¹M, except Cu(NO₃)₂, which was 2 × 10⁻²M. The pH of the solution was adjusted with HCl or NaOH to the values described in the text.

General Procedure

To 0.5 ml of CF-G or CF-S solution, 0.25 ml of water (or 5 × 10⁻²M tris buffer, pH 7) was added. At 37°, the solution was mixed with 0.25 ml of a metal nitrate solution, which was warmed at 37° and incubated. After 15, 30, 60, 90, and 120 minutes, 8 μl of the solution was injected into a high speed liquid chromatograph according to the condition reported before.⁶⁾

1) Location: Hongo, Bunkyo-ku, Tokyo.

2) M. Hayashi, T. Fuwa, S. Awazu, and M. Hanano, *Chem. Pharm. Bull.* (Tokyo), **23**, 2174 (1975).

3) C.R. Clark and R.W. Hay, *Chem. Commun.*, **1970**, 794.

4) R.W. Hay and J.A.G. Edmonds, *Chem. Commun.*, **1967**, 969.

5) K. Nagasawa and H. Yoshidome, *Chem. Pharm. Bull.* (Tokyo), **21**, 903 (1973).

6) C.T. Chen, K. Hayakawa, T. Imanari, and Z. Tamura, *Chem. Pharm. Bull.* (Tokyo), **23**, 2174 (1975).

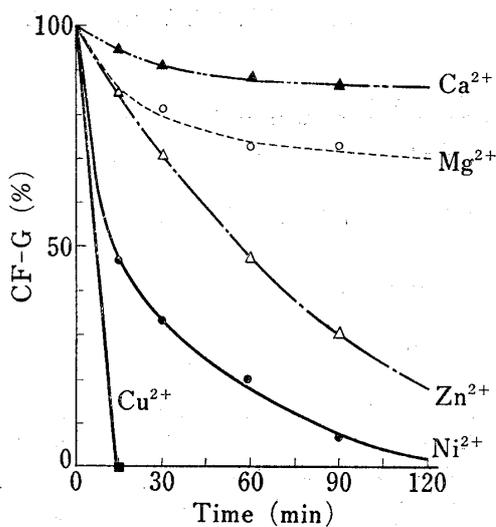


Fig. 1. Hydrolysis of CF-G with Metal Ions at pH 7

final concentrations: CF-G; $5 \times 10^{-4}M$,
 $Ca(NO_3)_2$, $Mg(NO_3)_2$, $Zn(NO_3)_2$ and $Ni(NO_3)_2$;
 $2.5 \times 10^{-2}M$ $Cu(NO_3)_2$; $5 \times 10^{-3}M$

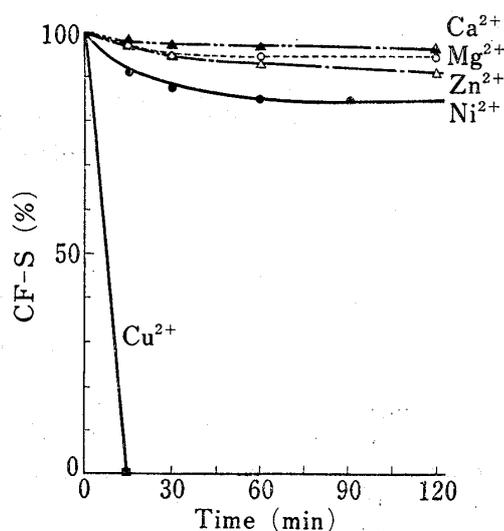


Fig. 2. Hydrolysis of CF-S with Metal Ions at pH 7

final concentrations: CF-S; $5 \times 10^{-4}M$
 $Ca(NO_3)_2$, $Mg(NO_3)_2$, $Zn(NO_3)_2$ and $Ni(NO_3)_2$;
 $2.5 \times 10^{-2}M$ $Cu(NO_3)_2$; $5 \times 10^{-3}M$

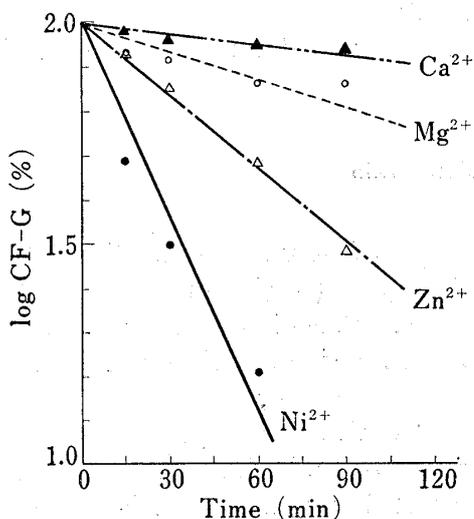


Fig. 3. Pseudo-first-order Plots of Data in Fig. 1

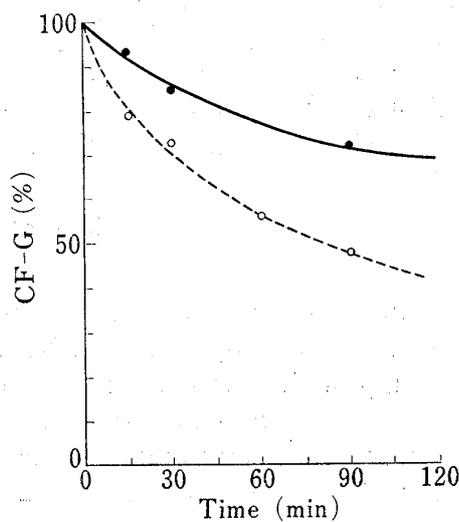


Fig. 4. Hydrolysis with Ni^{2+} at pH 7 in the Presence (—●—) and in the Absence (---○---) of Tris Buffer

final concentrations: CF-G; $5 \times 10^{-4}M$
 $Ni(NO_3)_2$; $2.5 \times 10^{-2}M$
 Tris; $1.25 \times 10^{-2}M$

TABLE I. Hydrolysis Rates (%) of CF-G and CF-S with Ni^{2+} at pH 2, 5, and 7

Incubation time (min)	CF-G			CF-S		
	pH 2	pH 5	pH 7	pH 2	pH 5	pH 7
15	9	40	53	0	4	9
30	13	54	67	0	6	13
60	16	74	79	0	6	14
90	17	87	93	0	7	14

final concentrations: CF-G or CF-S; $5 \times 10^{-4}M$ $Ni(NO_3)_2$; $2.5 \times 10^{-2}M$

Results and Discussion

Both CF-G and CF-S were hydrolyzed in water at pH 7 in the presence of metal ions (Fig. 1, Fig. 2). It was noteworthy that in this condition, CF-G was hydrolyzed more easily than CF-S, although in the case of Cu^{2+} , hydrolysis was too fast to be compared.

The rate of hydrolysis was in parallel with the stability constants of 8-quinolinol-metal complexes ($\text{Cu}^{2+} > \text{Ni}^{2+} > \text{Zn}^{2+} > \text{Mg}^{2+} > \text{Ca}^{2+}$). Similarly to Cu^{2+} -catalyzed hydrolysis of glucoside³⁾ or sulfate⁴⁾ of 8-quinolinol, the pseudo-first order rate reaction was observed with CF-G (Fig. 3).

Contrary to the acid hydrolysis, the rate of metal catalyzed hydrolysis of the conjugates increased with reduction of concentration of H^+ as shown in Table I. When pH was above 7, the precipitates of hydroxide disturbed the hydrolysis.

It has been proposed that Cu^{2+} -catalyzed hydrolysis of glucoside³⁾ or sulfate⁴⁾ of 8-quinolinol was derived from its formation of complex with Cu^{2+} . In this experiment phenolphthalein mono-glucuronide, as a reference, was not hydrolyzed with those metal ions. Moreover tris buffer suppressed the hydrolysis of CF-G (Fig. 4). These results suggest that the similar character of CF causes the hydrolysis of CF-G and CF-S with metal ions.

It is interesting that metal compounds were prescribed with many SMON (Subacute-myelo-optico-neuropathy) patients.⁷⁾ The possibility that CF conjugates, which have been once produced in a body, are hydrolyzed again in the presence of metal ions, is worthy of consideration.

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7) T. Sobue and K. Ando, *Igaku no Ayumi*, (Japan), **77**, 734 (1971).