

750. *Studies on Girard-hydrazones. Part I. Kinetic Study on the Hydrolysis of the Girard-hydrazone of Cyclopentanone.*

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The acid-catalysed hydrolysis of cyclopentanone Girard-hydrazone has been studied kinetically in aqueous solution (10% ethanol) (pH 1—8) by a polarographic method. Measurable accumulation of an intermediate was not detected. The rate of the hydrolysis at zero concentration of buffer is of first-order with respect to $[H^+]$ in two pH regions. Only a mechanism based on a steady-state assumption for an intermediate could explain the pH-rate profile obtained satisfactorily. The theoretical curve is in good agreement with the experimental plots.

GIRARD-HYDRAZONE has been used for the separation of aldehydes and ketones, and of keto-steroids.¹ Though the separation is based on the difference in hydrolysis rate of the hydrazones, the mechanisms of the hydrolysis have been little studied kinetically. The kinetic treatment is restricted to comparison of the rate constants of various compounds at a few pH values.¹ For the mechanisms of the hydrolysis, an amino-alcohol was suggested as intermediate, merely by analogy with the hydrolysis of other azomethine groups.² Girard-hydrazone is also used for the polarographic determination of difficultly reducible carbonyl compounds, and its polarographic behaviour has been studied.^{3,4}

The reported interpretation of the electrode reaction is not entirely acceptable, but the linear relation between wave height and concentration in dilute solution is useful for following the hydrolysis. Electrochemical study of the hydrolysis may also give valuable information on the electrode behaviour of the compound.

On hydrolysis of an azomethine group, as in its formation, an amino-alcohol is considered to be the intermediate,⁵ and because of the transition in rate-determining step with changing $[H^+]$, an inflection was said to arise in the pH-rate profile.⁶ However, few such profiles have been studied experimentally with one compound and one solvent system, because of the very large difference for the reaction rate in the rather wide range of proton concentration. We examined about thirty Girard-hydrazones before selecting cyclopentanone Girard-hydrazone for study.

EXPERIMENTAL

Materials.—All materials were of reagent grade unless otherwise specified. Girard reagent τ (Merck, G.R.) was used without further purification after being dried in a vacuum desiccator for 2—3 hr. Cyclopentanone (Tokyo Kasei) was purified by distillation (b. p. 23—25/10 mm.). The stock solution of the Girard-hydrazone was prepared essentially as described by Prelog.³

¹ Wheeler, *Chem. Rev.*, 1962, **62**, 205.

² Wheeler and Rosado, *Tetrahedron*, 1962, **18**, 477.

³ Prelog and Häfliger, *Helv. Chim. Acta*, 1949, **32**, 2088.

⁴ Young, *J.*, 1955, 1516.

⁵ Kastening, Holleck, and Melkonian, *Z. Elektrochem.*, 1956, **60**, 130, footnote 13.

⁶ Cordes and Jenks, *J. Amer. Chem. Soc.*, 1962, **84**, 832.

and by Young *et al.*⁴ It contained about $5 \times 10^{-3}M$ of Girard-hydrazone. Ethanol was treated with 2,4-dinitrophenylhydrazine to eliminate aldehyde before use. No measurable decomposition of the hydrazone, in the stock solution, was detected during 3 weeks by polarography.

Buffer Solutions.—McIlvaine-type buffer system was used for pH 2—8. For solutions more acid than pH 2, HCl-KCl was used. The ionic strength of the solution was adjusted to 0.5 by adding potassium chloride, according to Elving *et al.*⁷ To extrapolate to zero concentration of buffer, these solutions were diluted, and the ionic strength and the pH values were re-adjusted by adding potassium chloride and hydrochloric acid or sodium hydroxide solution. For the additional experiments in the range above pH 8, Britton-Robinson type buffer solutions, containing 0.1M-potassium chloride, were used.

Apparatus.—Polarographic measurements were made with a Yanagimoto type AP-1 potential scanner and GR-3 Galvarecoder at $25 \pm 0.1^\circ$. The dropping-mercury electrode had a value of $m^{2/3}t^{1/6} = 1.12 \text{ mg.}^{2/3} \text{ sec.}^{-1/2}$. pH values were measured by a Töadempa model HM-5 pH meter with glass-saturated calomel electrode.

Kinetic Measurements.—The concentration of unchanged hydrazone was determined polarographically. In the whole pH range studied, the polarogram gave a linear current-concentration relation up to about $5 \times 10^{-4}M$. For the experiments above pH 3, the stock solution (2.5 ml.) was mixed in a stoppered-flask with buffer solution (22.5 ml.) at $25 \pm 0.1^\circ$, and stored at the same temperature. The initial concentration of the hydrazone was about $5 \times 10^{-4}M$. A portion of the solution was removed by pipette at suitable intervals and analysed polarographically after being deoxygenated by nitrogen for about 3 min. The test solution contained 0.01% gelatine as a maximum suppressor. The gelatine produced no detectable effect for the hydrolysis rate at the concentration. The pH of the test solution was estimated on a separate solution prepared just like the test solution but without the hydrazone.

For runs below pH 3, the method of Kastening *et al.*⁵ was used, because the rate was too fast to record on a polarogram. The deoxygenated stock solution was added to the deoxygenated buffer solution at $25 \pm 0.1^\circ$ beforehand in a electrolysis cell; the cell is composed of a four-necked flask, mercury-pool electrode, dropping-mercury electrode, gas inlet and outlet, and a stock-solution supplier. Mixed by nitrogen-bubbling for a short time, the resulting solution was subjected to a polarographic measurement at a constant potential. The test solution was initially about $5 \times 10^{-4}M$ in the hydrazone and 0.01% in gelatine.

RESULTS

The polarograms of cyclopentanone Girard-hydrazone are shown in Fig. 1. For a first-order reaction, the rate constant was obtained from the polarographic wave height according to the equation:⁸

$$kt/2.303 = \log [(i_0 - i_\infty)/(i - i_\infty)]$$

$$\text{or} \quad kt/2.303 + \log(i - i') = \log[(i_0 - i_\infty)(1 - e^{-k\Delta})] = \text{constant}$$

where i_0 , i_∞ , i , and i' are the wave heights at zero time, infinite time, t and t' , where $t' = t + \Delta$, in which Δ is a constant time interval. Therefore, from the slope of the plot of $\log(i - i_\infty)$ or $\log(i - i')$ against time t , an observed first-order rate constant is obtained. Examples at pH 5.48, 6.78, and 2.12 are shown in Fig. 2. The strict linearity throughout any run confirms the pseudo-first-order kinetics at each pH value. The observed rate constant is a linear function of the buffer concentration, as shown in Fig. 3. The pseudo-first-order rate constants shown in the Table as k_a were obtained by extrapolation to zero concentration of buffer. When

Apparent rate constants of hydrolysis of cyclopentanone Girard-hydrazone; at 25°
and ionic strength 0.5M.

pH	1.04	1.31	1.51	1.71	2.12	2.64	3.06	3.44
k_a (min. ⁻¹)	2.65	1.35	1.00	6.10×10^{-1}	2.62×10^{-1}	1.0×10^{-1}	3.5×10^{-2}	1.0×10^{-2}
pH		4.44	5.44	5.77	6.14	6.17	6.78	7.58
k_a (min. ⁻¹)		6.0×10^{-3}	4.2×10^{-3}	3.5×10^{-3}	$2.3_5 \times 10^{-3}$	2.0×10^{-3}	8.0×10^{-4}	5.5×10^{-4}
pH 1.04—2.12: Runs in KCl-HCl. pH 2.64—7.58: Extrapolated to zero concentration of buffer.								

⁷ Elving, Markowitz, and Rosenthal, *Analyt. Chem.*, 1956, **28**, 1179.

⁸ Frost and Pearson, "Kinetics and Mechanisms," John Wiley and Sons, Inc., New York, 1961, ch. 3.

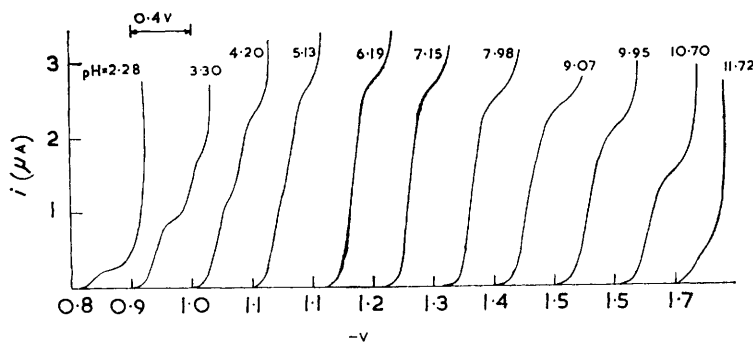


FIG. 1. Polarograms of cyclopentanone Girard-hydrazone measured at 5 minutes after preparation (initial concn. $5 \times 10^{-4}M$, $\mu = 0.5M$, at 25°).

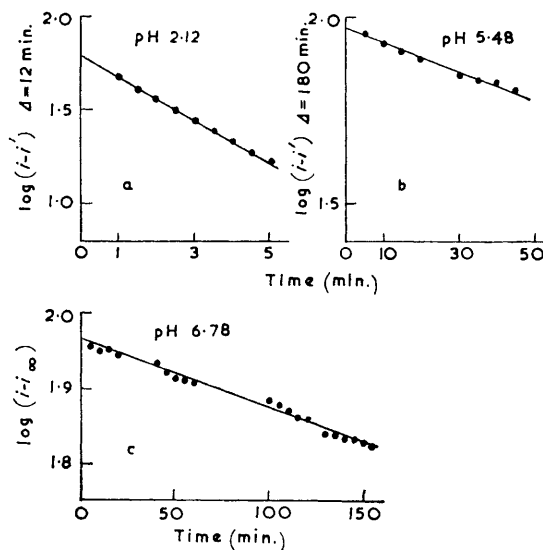


FIG. 2. Examples of polarographic determination of a rate constant (initial concentrations: (a) $2 \times 10^{-4}M$, (b) and (c) $5 \times 10^{-4}M$; $\mu = 0.5M$, at 25°).

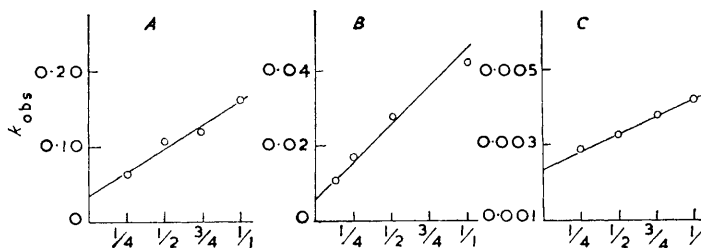


FIG. 3. Effect of McIlvaine buffer concentration on the rate (concentrations are shown by ratios; $\mu = 0.5M$, at 25°).

A, pH 3.06; B, pH 4.44; C, pH 6.14.

$\log k_a$ is plotted against pH a pH-rate profile shown in Fig. 4 is obtained. This shows that the rate is of first-order with respect to hydrogen-ion concentration in two different pH regions. Between pH 8 and 12, no noticeable change in the rate was observed. Hydroxyl-ion catalysis is therefore neglected in the whole region studied.

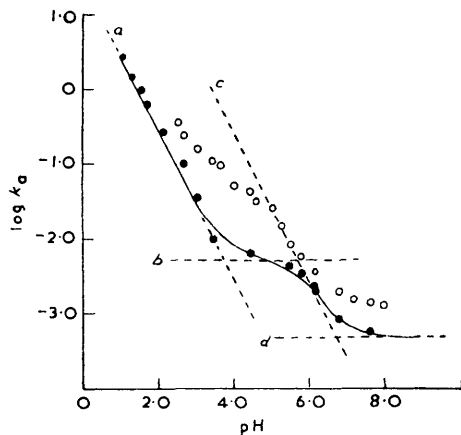
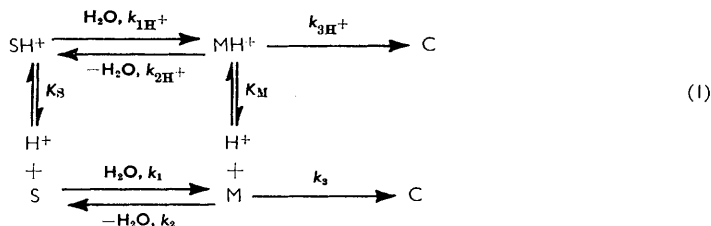


FIG. 4. The hydrolysis of cyclopentanone Girard-hydrazone as a function of pH. ($\mu = 0.5M$, at 25° .)

- Obtained at zero concentration of buffer.
- In McIlvaine type buffer.
- Calculated curve (equation 17).
- - - Calculated curve (equations 12—15).

DISCUSSION

The pH-rate profile obtained for the hydrolysis of cyclopentanone Girard-hydrazone between pH 1 and 8 at 25° is similar to those reported for the Schiff base by Willi⁹ and Cordes and Jencks.⁶ Cordes and Jencks reported a transition in rate-determining step as the pH of the medium is changed. In the present study, an amino-alcohol intermediate, considered the most probable intermediate in the hydrolysis of azomethine groups, is also considered, and Scheme (1) is advanced to interpret the pH-rate profile shown in Fig. 3:



where S = cyclo-C₅H₈N·NH·CO·CH₂·NMe₃⁺Cl⁻; SH⁺ = protonized S; M = 1-HO-cyclo-C₅H₈NH·NH·CO·CH₂·NMe₃⁺Cl⁻; MH⁺ = protonized M; C = products; and $k_{1\text{H}^+}$, k_1 , etc., represent the rate constant for each step.

$$\text{By introduction of } x = [\text{S}] + [\text{SH}^+]; y = [\text{M}] + [\text{MH}^+]; \text{ and } z = [\text{C}] \quad (2)$$

we have:

$$dx/dt = -k_{1\text{H}^+}[\text{SH}^+] - k_1[\text{S}] + k_{2\text{H}^+}[\text{MH}^+] + k_2[\text{M}]$$

$$dy/dt = k_{1\text{H}^+}[\text{SH}^+] + k_1[\text{S}] - k_{2\text{H}^+}[\text{MH}^+] - k_2[\text{M}] - k_{3\text{H}^+}[\text{MH}^+] - k_3[\text{M}] \quad (3)$$

$$dz/dt = k_{3\text{H}^+}[\text{MH}^+] + k_3[\text{M}]$$

where the reverse reaction of $\text{MH}^+ \rightarrow \text{C}$ and $\text{M} \rightarrow \text{C}$, formation of hydrazone, is neglected, because the initial concentration of x is $5 \times 10^{-4}M$ and the equilibrium between the hydrazone and its components exists almost completely on the components-side as was shown experimentally by the negligible wave height at infinite time. K_S and K_M in eqn. (1) become

$$K_S = \frac{[\text{SH}^+]}{[\text{S}][\text{H}^+]} = \frac{1}{K_a} \text{ and } K_M = \frac{[\text{MH}^+]}{[\text{M}][\text{H}^+]} \quad (4)$$

⁹ Willi, *Helv. Chim. Acta*, 1956, **39**, 1193.

where K_a is the dissociation constant for the conjugate acid of the Girard-hydrazone. The value of K_a was not known experimentally, but the magnitude is expected to be larger than 10^{-1} from preliminary titration of benzophenone Girard-hydrazone, and from the fact that the pH-independent region for the rate constant below the pH corresponding to the pK_a value,^{6,10} was not observed down to pH 1. Benzophenone Girard-hydrazone was selected for the titration because of its stability in acid solution. The order of K_S is, therefore, assumed to be smaller than 10.

From eqns. (2) and (4) the followings are derived:

$$[\text{SH}^+] = \frac{K_S[\text{H}^+]}{1 + K_S[\text{H}^+]} x, [\text{S}] = \frac{1}{1 + K_S[\text{H}^+]} x,$$

$$[\text{MH}^+] = \frac{K_M[\text{H}^+]}{1 + K_M[\text{H}^+]} y, [\text{M}] = \frac{1}{1 + K_M[\text{H}^+]} y \quad (5)$$

Putting (5) into (3), we obtain

$$\begin{aligned} dx/dt &= -k_x x + k_x y \\ dy/dt &= k_x x - k_y y - k_z y \\ dz/dt &= k_z y \end{aligned} \quad (6)$$

where

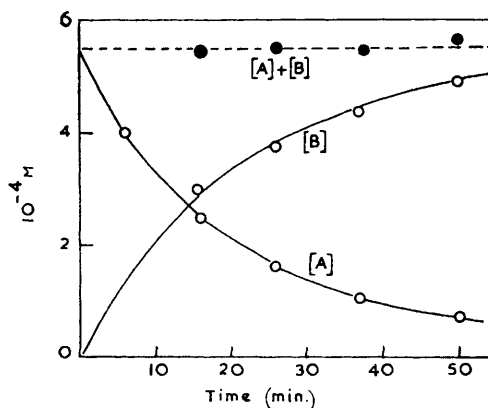
$$\begin{aligned} k_x &= k_{1\text{H}^+} \frac{K_S[\text{H}^+]}{1 + K_S[\text{H}^+]} + k_1/(1 + K_S[\text{H}^+]) \\ k_y &= k_{2\text{H}^+} \frac{K_M[\text{H}^+]}{1 + K_M[\text{H}^+]} + k_2/(1 + K_M[\text{H}^+]) \\ k_z &= k_{3\text{H}^+} \frac{K_M[\text{H}^+]}{1 + K_M[\text{H}^+]} + k_3/(1 + K_M[\text{H}^+]) \end{aligned} \quad (7)$$

Therefore, the reaction scheme is reduced to



Since the disappearance of X was followed and found to be of pseudo-first-order, two kinetic treatments may be possible; one is a steady-state treatment about Y as was

FIG. 5. Variation of the concentration of [A] acetophenone Girard-hydrazone, and [B] acetophenone, with time (at pH 3.05, and $\mu = 0.5\text{M}$). Initial concentrations: [A], $5.5 \times 10^{-4}\text{M}$, [B] = 0.



carried out by Willi⁹ and Reeves,¹⁰ and the other is that which makes only the step $Y \rightarrow Z$ rate-determining, on the assumption that k_x and $k_y \gg k_z$, as carried out by Kastening, Holleck, and Melkonian.⁵ However, by the latter treatment, the pH-rate profile obtained was not satisfactorily explained. No distinct indication^{5,10} could be obtained from experiments carried out on acetophenone Girard-hydrazone (Fig. 5) for the accumulation

¹⁰ Reeves, *J. Amer. Chem. Soc.*, 1962, **84**, 3332.

of the amino-alcohol intermediate by a slow process. This hydrazone was used as a model compound for this purpose, because acetophenone produced by the hydrolysis is determinable simultaneously by polarography. We, therefore, applied a steady-state method to the present study.

From the steady-state approximation,

$$dy/dt = k_x x - k_y y - k_z y = 0$$

so that

$$y = k_x x / (k_y + k_z)$$

Then

$$dx/dt = -k_x k_z x / (k_y + k_z) \quad (9)$$

Since

$$k_{1H^+} \gg k_1, k_{2H^+} \gg k_2, k_{3H^+} \gg k_3 \quad (10)$$

for the acid-catalysed reaction, the following four situations can be considered when $[H^+]$ is changing from large to small, without contravention of the steady-state assumption.

$$\begin{array}{ll} (a) & k_{1H^+} K_S [H^+] \gg k_1 \\ & (k_{3H^+} + k_{2H^+}) K_M [H^+] \gg k_2 \\ & k_{3H^+} K_M [H^+] \gg k_3 \\ (c) & k_{1H^+} K_S [H^+] \ll k_1 \\ & (k_{3H^+} + k_{2H^+}) K_M [H^+] \ll k_2 \\ & k_{3H^+} K_M [H^+] \gg k_3 \\ (b) & k_{1H^+} K_S [H^+] \ll k_1 \\ & (k_{3H^+} + k_{2H^+}) K_M [H^+] \gg k_2 \\ & k_{3H^+} K_M [H^+] \gg k_3 \\ (d) & k_{1H^+} K_S [H^+] \ll k_1 \\ & (k_{3H^+} + k_{2H^+}) K_M [H^+] \ll k_2 \\ & k_{3H^+} K_M [H^+] \ll k_3 \end{array}$$

When the hydrogen-ion concentration is so large that the additional condition $K_S [H^+] \gg 1$ is satisfied, (a) should be considered. From eqns. (7) and (9), and the above conditions, we obtain

$$dx/dt = x k_{1H^+} k_{3H^+} / (k_{2H^+} + k_{3H^+})$$

so that the reaction rate is independent of $[H^+]$. Because the reaction is too fast to measure by ordinary methods in solution more acid than pH 1, the existence of the region was not shown experimentally, but may be assumed from reported results on other azo-methines.^{6,10} In the pH region studied in this Paper, therefore, the condition

$$K_S [H^+] \ll 1 \quad (11)$$

should hold.

Equations (12), (13), (14), and (15) are derived, respectively, from eqns. (7), (9), and (10) for the four situations (a)—(d):

$$dx/dt \simeq - \frac{k_{1H^+} k_{3H^+}}{k_{2H^+} + k_{3H^+}} K_S [H^+] x \quad (12)$$

$$dx/dt \simeq - \frac{k_1 k_{3H^+}}{k_{2H^+} + k_{3H^+}} x \quad (13)$$

$$dx/dt \simeq - \frac{k_1 k_{3H^+}}{k_2} K_M [H^+] x \quad (14)$$

$$dx/dt \simeq - \frac{k_1 k_3}{k_2 + k_3} x \quad (15)$$

It is apparent from these equations that the reaction rate varies linearly with $[H^+]$ for (a) and (c), whereas the rate is independent of hydrogen-ion concentration for (b) and (d). The pH-rate profile, therefore, should appear as the dotted lines in Fig. 4 (though the position is arbitrary), if the conditions are strictly realized. The experimental plots (solid circles in Fig. 4) follow the theoretical curve quite closely in shape.

Under the same condition, putting eqn. (7) into (9), we obtain

$$k_a = \frac{k_1 k_3 + (k_1 k_{3H} + K_M + k_3 k_{1H} + K_S)[H^+] + k_{1H} + k_{3H} + K_S K_M [H^+]^2}{(k_2 + k_3) + (k_{2H} + k_{3H}) K_M [H^+]} \quad (16)$$

This equation can be expressed as (17)

$$k_a = \frac{k_0 + k_I [H^+] + k_{II} [H^+]^2}{k_{III} + [H^+]} \quad (17)$$

which is of the same form as the rate law of Willi⁹ and Reeves.¹⁰ Adjusting this equation to fit the experimental plots, we obtain

$$k_0 = 8.87 \times 10^{-10} \quad k_I = 5.20 \times 10^{-3} \quad k_{II} = 2.75 \times 10 \quad k_{III} = 2.03 \times 10^{-6}$$

When these values are used, the variation of k_a with $[H^+]$, calculated by eqn. (17), is represented as the solid line in Fig. 4. When we assume that $k_2 \gg k_3$ [this is derived from (c)], and

$$k_1 k_{3H} + K_M \gg k_3 k_{1H} + K_S \quad (18)$$

we obtain (19) from (16) and (17).

$$\begin{aligned} k_{1H} + k_{3H} + K_S / (k_{2H} + k_{3H}) &= k_{II} = 2.75 \times 10 & k_1 k_{3H} / (k_{2H} + k_{3H}) &= k_I = 5.20 \times 10^{-3}, \\ k_1 k_{3H} + K_M / k_2 &= k_I / k_{III} = 2.56 \times 10^3 & k_1 k_3 / k_2 &= k_0 / k_{III} = 4.37 \times 10^{-4} \end{aligned} \quad (19)$$

With these values, we get the four straight lines, *a*, *b*, *c*, and *d*, shown as dotted lines in Fig. 4, from eqns. (12), (13), (14), and (15), respectively. The data, therefore, establish the relations introduced in the conditions (a), (b), (c), and (d), and others. Other assumptions may be possible for eqn. (18), but this was found to be the most satisfactory.

From these discussions, we conclude for the hydrolysis of the Girard-hydrazone that the formation of MH^+ or *M* and its decomposition both contribute as rate-determining steps, but the fastest rate is $SH^+ \rightleftharpoons MH^+$ and the slowest is $M \rightarrow C$.

General acid catalysis is observed for the whole pH range if McIlvain's buffer solution is used. The observed rate constants, including the general acid catalysis, are shown by open circles in Fig. 4. Reeves¹⁰ suggested (A) for the transition state in the hydrolysis of



Schiff base. Similarly, we suggest (B) as the transition state for the amino-alcohol, where X is water or an acid anion.

The degree of contribution of each reaction as rate determining is not known from this kinetic work, but the change, with the change in $[H^+]$, in the rate-determining step from the formation of amino-alcohol to its decomposition, claimed for the hydrolysis of a Schiff base, seems incorrect for the Girard-hydrazone.

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