Oxidation of Flavoxate by Chloramine-T in HCl Medium, a Kinetic and Mechanistic Approach

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Abstract

The kinetics of oxidation of flavoxate (FX) by sodium-N-chloro-p-toluenesuphonamide or chloramine-T (CAT) has been carried out in acid medium at 303K. The reaction rate shows a first order dependence on [oxidant], fractional order on [substrate] and an inverse fractional order on [H^+]. The addition of the reaction product (p-toluenesulphonamide) and halide ions have no significant effect on the rate of the reaction. The variation of ionic strength of the medium did not affect the rate, indicating that non ionic species are involved in the rate determining step. The dielectric effect is negative. The reaction fails to initiate the polymerization of acrlyamide. Thermodynamic parameters were computed by studying the reaction at different temperatures. The reaction stoichiometry and oxidation products were identified. Activation parameters for the rate-limiting step have been computed. Based on the experimental observations a suitable mechanism was proposed and rate law deduced.

Keywords: Kinetics, oxidation, chloramine-T, flavoxate, acid medium.

Introduction

The chemistry of N-haloamines has received considerable attention because of their versatility in behaving as mild oxidants, halogenating agents and N-anions, which act both as bases and nucleophiles[1-4]. These compounds react with a wide range of functional groups and affect a variety of molecular changes. Chloramine-T (CAT) is a prominent member of this class which is a by-product in the manufacture of saccharin and is a well known oxidizing and chlorinating reagent both in acidic and alkaline media. Mechanistic aspects of these reactions have been documented[5,6]. However, survey of literature indicates limited information available on the oxidation of pharmaceuticals with CAT. Kinetic study has also been carried out using other oxidants[7].
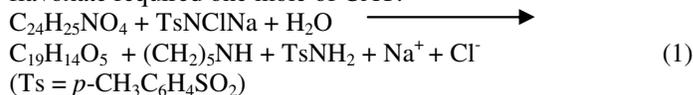
Flavoxate (2-(-1-piperidyl)ethyl 3-methyl-4-oxo-2-phenyl-chromene -8-carboxylate) is used to treat spasms in the urinary tract or difficult urination and is taken in combination with antibiotics to treat the infection. Flavoxate hydrochloride, is a muscle relaxant and it works by relaxing the involuntary muscle that is found in the wall of the bladder[8].

A review of literature shows that there is no information available on the kinetics and oxidation of flavoxate by any oxidizing agents from the mechanistic view point. There was a need for understanding the mechanism of oxidation of flavoxate. This study may throw some light on the metabolic conversions in the biological system. Hence in the present communication, the kinetics and mechanistic aspects of the oxidation of flavoxate by chloramine-T in HCl medium at 303K has been investigated.

Material and Methods

An aqueous solution of CAT (E.Merck) was prepared, standardized iodometrically and stored in brown bottles to prevent any photochemical deterioration. The substrate flavoxate (Biocon Ltd) was used as received. The aqueous solution of the substrate was prepared freshly each time. All the other chemicals used were of analytical grade. Doubly distilled water was used for all the measurements. The reactions were carried out under pseudo- first order conditions by keeping an excess of flavoxate over CAT. Solutions containing appropriate amounts of FX, HCl and water (to keep the total volume constant for all runs) were taken in a glass-stoppered pyrex boiling tube, and thermostated at 303K. A measured amount of CAT solution, also thermostated at the same temperature, was rapidly added to the mixture. The progress of the reaction was monitored by iodometric estimation of unreacted CAT in a measured aliquot (5ml) of the mixture at different time intervals. The course of the reaction was studied up to 75 to 80% completion. The rate constants were evaluated from the plots of log [CAT] against time. The pseudo- first order rate constants (k') calculated were reproducible within $\pm$ 4%.

Stoichiometry and Product Analysis: Varying ratios of flavoxate and chloramine-T were equilibrated in the presence of 5.0 x10^{-3} mol dm^{-3} HCl for 24h at 303 K. Determination of unreacted CAT in the reaction mixture showed that one mole of flavoxate required one mole of CAT.

$$C_{24}H_{25}NO_4 + TsNClNa + H_2O \longrightarrow$$
$$C_{19}H_{14}O_5 + (CH_2)_5NH + TsNH_2 + Na^+ + Cl^- \qquad (1)$$
$$(Ts = p\text{-}CH_3C_6H_4SO_2)$$

The reduction product of oxidant, *p*-toluenesulphonamide was detected by thin layer chromatography using light petroleum ether, chloroform and 1- butanol (2:2:1v/v/v) as the solvent and iodine as the reducing agent[9]. The reported R_f value is consistent with the given R_f value in the literature. It was further confirmed by its melting point, IR and NMR spectral studies. Analysis revealed the formation of the oxidation product of flavoxate to be 2-oxoethyl 3-methyl-4-oxo-2-phenyl-4H-chromene -8-carboxylate. The presence of the aldehyde group was detected by their 2,4-DNP derivatives. It was further confirmed by IR spectroscopy which shows a strong peak at 1700 cm^{-1} and 2820cm^{-1}. The other product piperidine was identified by spot tests[10].

Results and Discussion

Effect of varying reactant concentrations on the reaction rate: Under pseudo-first order conditions, with the substrate in excess, at constant [FX], [HCl] and constant temperature, plots of log [CAT] versus time were linear indicating a first order dependence of the reaction rate on [CAT]$_0$. Values of pseudo-first order rate constant ($k^/$) are given in table 1. Further it was found that these values are unaffected by a variation of [CAT]$_0$, confirming the first order dependence on [oxidant]. Under identical experimental conditions, an increase in [FX]$_0$ increased the $k^/$ values as shown in table 1. In figure 1, a plot of log $k^/$ versus log[FX] was linear with a slope of 0.50, showing a fractional order dependence of the rate on [FX]$_0$.

The rate of the reaction decreases with the increase in [HCl] as reported in table 1. In figure 1, a plot of log $k^/$ versus log [HCl] was linear with a negative slope of 0.60 indicating a negative fractional order dependence of the rate on [HCl].

Table–1
Effect of varying reactant concentrations

10^4 [CAT]$_0$ (mol dm^{-3})	10^3 [FX] (mol dm^{-3})	10^3 [HCl] (mol dm^{-3})	$10^4 k^/$ (s^{-1})
2.0	10.0	5.0	3.90
5.0	10.0	5.0	3.92
10.0	10.0	5.0	3.90
20.0	10.0	5.0	3.89
10.0	2.0	5.0	1.12
10.0	5.0	5.0	2.17
10.0	10.0	5.0	3.90
10.0	20.0	5.0	5.62
10.0	10.0	2.0	6.02
10.0	10.0	5.0	3.91
10.0	10.0	10.0	2.95
10.0	10.0	20.0	2.24

I = 0.5 mol dm^{-3} ; T = 303K

Effect of halide ions on the reaction rate: The addition of NaBr and NaCl (1.0×10^{-3} - 10.0×10^{-3} mol dm^{-3}) showed negligible effect on the rate of the reaction. This clearly confirms that the rate of the reaction is retarded only by H$^+$ ions.
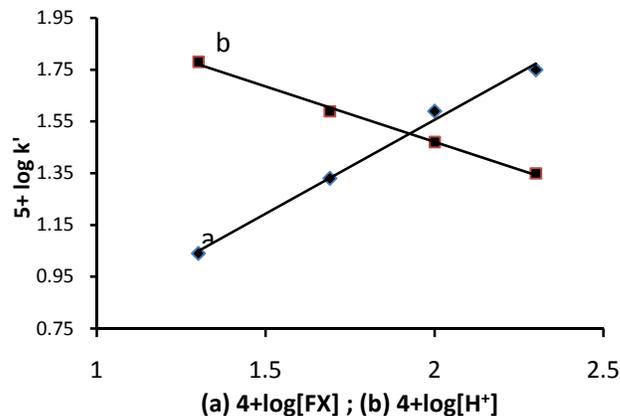

Figure–1
Effect of [FX] and [H$^+$] on the rate of the reaction

Effect of p-toluenesulphonamide on the reaction rate: The addition of reduction product, *p*-toluenesulphonamide (1.0×10^{-3}-10.0×10^{-3} mol dm^{-3}) has a negligible effect on the reaction rate. This indicated the non involvement of PTS in a pre-equilibrium with the oxidant.

Effect of ionic strength on the reaction rate: The variation of ionic strength (I) of the medium using NaClO$_4$ solution (1×10^{-3}-10×10^{-3}moldm^{-3}) showed no effect on the reaction rate, indicating that non-ionic species are involved in the rate limiting step.

Effect of varying dielectric constant of medium on the reaction rate: The dielectric constant of the medium was varied by adding methanol [0 – 30% v/v] to the reaction mixture. The rate was found to decrease with increase in methanol content as seen in table 2. In figure-2, a plot of log$k^/$ versus 1/D gave a negative slope of 0.75, supporting a rate limiting step involving partial ionization. D is the dielectric permittivity of the medium, whose values were taken from the literature[11]. Blank experiments with methanol, showed that there was slight decomposition (<3%) of solvent under the given experimental condition. This was corrected for the calculation of net reaction rate constant for the oxidation of flavoxate.

Table–2
Effect of varying dielectric constant of the medium

MeOH % v/v	D	10^2/D	$10^4 k^/$ (s^{-1})
0	76.73	1.30	3.90
10	72.37	1.38	3.32
20	67.38	1.46	2.82
30	62.71	1.60	2.30

[CAT]$_0$ =10.0×10^{-4}mol dm^{-3}, [FX]=10.0×10^{-3} mol dm^{-3}, [HCl] = 5.0×10^{-3}mol dm^{-3}, T=303K.

Effect of Temperature on the reaction rate: The reaction has been carried out at various temperatures (293- 323K) keeping other experimental conditions constant. From figure-3, the linear Arrhenius plot of log $k^/$ versus 1/T, values of activation parameters have been computed. These data are presented in table 3.
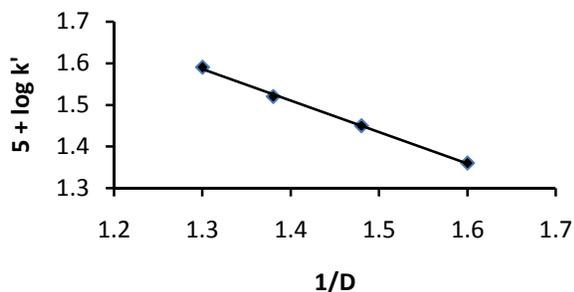
Figure-2
Effect of Dielectric constant of the medium on the rate of the reaction

Table–3
Effect of Temperature and Activation Parameters

Temperature (K)	$10^4 k'$ (s^{-1})	Activation Parameters	
		Parameter	Value
293	1.59(3.02)	E_a (kJmol^{-1})	55.56 (46.60)
303	3.90(8.55)	$\Delta H^{\#}$ (kJmol^{-1})	53.00 (44.08)
313	7.95(12.59)	$\Delta G^{\#}$ (kJmol^{-1})	93.90 (86.19)
323	13.80(19.06)	$\Delta S^{\#}$ (JK^{-1} mol^{-1})	-135.00 (-139.00)

$[BAT]_0 = 10.0 \times 10^{-4}$ mol dm^{-3}, $[FX] = 10.0 \times 10^{-3}$ mol dm^{-3}, $[HCl] = 5.0 \times 10^{-3}$ mol dm^{-3}, $I = 0.5$ mol dm^{-3}. Values in parenthesis are the decomposition constants and activation parameters for the rate determining step.
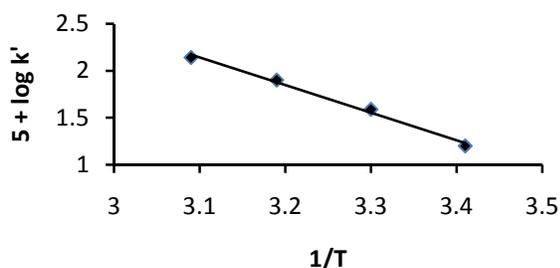

Figure-3
Effect of temperature on the rate of the reaction

Test for free radicals: Addition of the reaction mixtures to acrylamide did not initiate polymerisation which indicates the absence of free radical species in the reaction mixture.

Chloroamine-T behaves as a strong electrolyte in aqueous solution[12-14]. Depending on the pH of the medium CAT furnishes the following types of reactive species in solutions[15-17].

$$TsNClNa \rightleftharpoons TsNCl^- + Na^+ \qquad (2)$$

(Here Ts=p-CH$_3$C$_6$H$_4$SO$_2^-$)

$$TsNCl^- + H^+ \rightleftharpoons TsNHCl \qquad (3)$$
$$2\ TsNHCl \rightleftharpoons TsNH_2 + TsNCl_2 \qquad (4)$$
$$TsNCl_2 + H_2O \rightleftharpoons TsNHCl + HOCl \qquad (5)$$
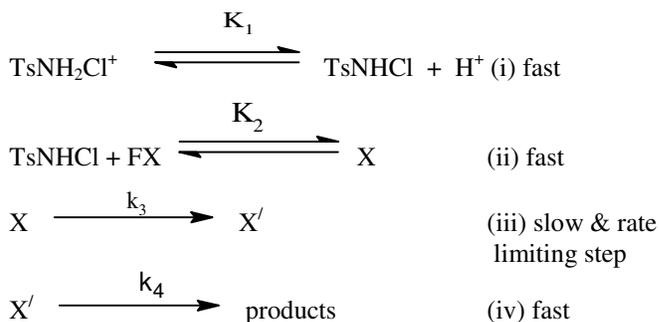$$TsNHCl + H_2O \rightleftharpoons TsNH_2 + HOCl \qquad (6)$$

The possible oxidizing species in acid medium are TsNHCl, TsNCl$_2$, HOCl. If TsNCl$_2$ were to be the reactive species, the rate law predicts a second order dependence of rate on [CAT] and a negative effect of TsNH$_2$ is expected according to equation 4, but both are contrary to the experimental observations. If HOCl is primarily involved, a first order retardation of the rate by the added benzenesulphonamide is expected. Since no such effect is noticed, HOCl can be ruled out as the oxidizing species. Hence, TsNHCl is the probable oxidising species for the oxidation of FX in acid medium. pH dependent relative concentrations of the species present in acidified haloamine solutions of comparable molarities have been studied which shows that TsNHCl is the possible oxidizing species in acid medium[15]. Monohaloamines can be further protonated at pH 2, as shown in equation 7 for chloramine-T[18].
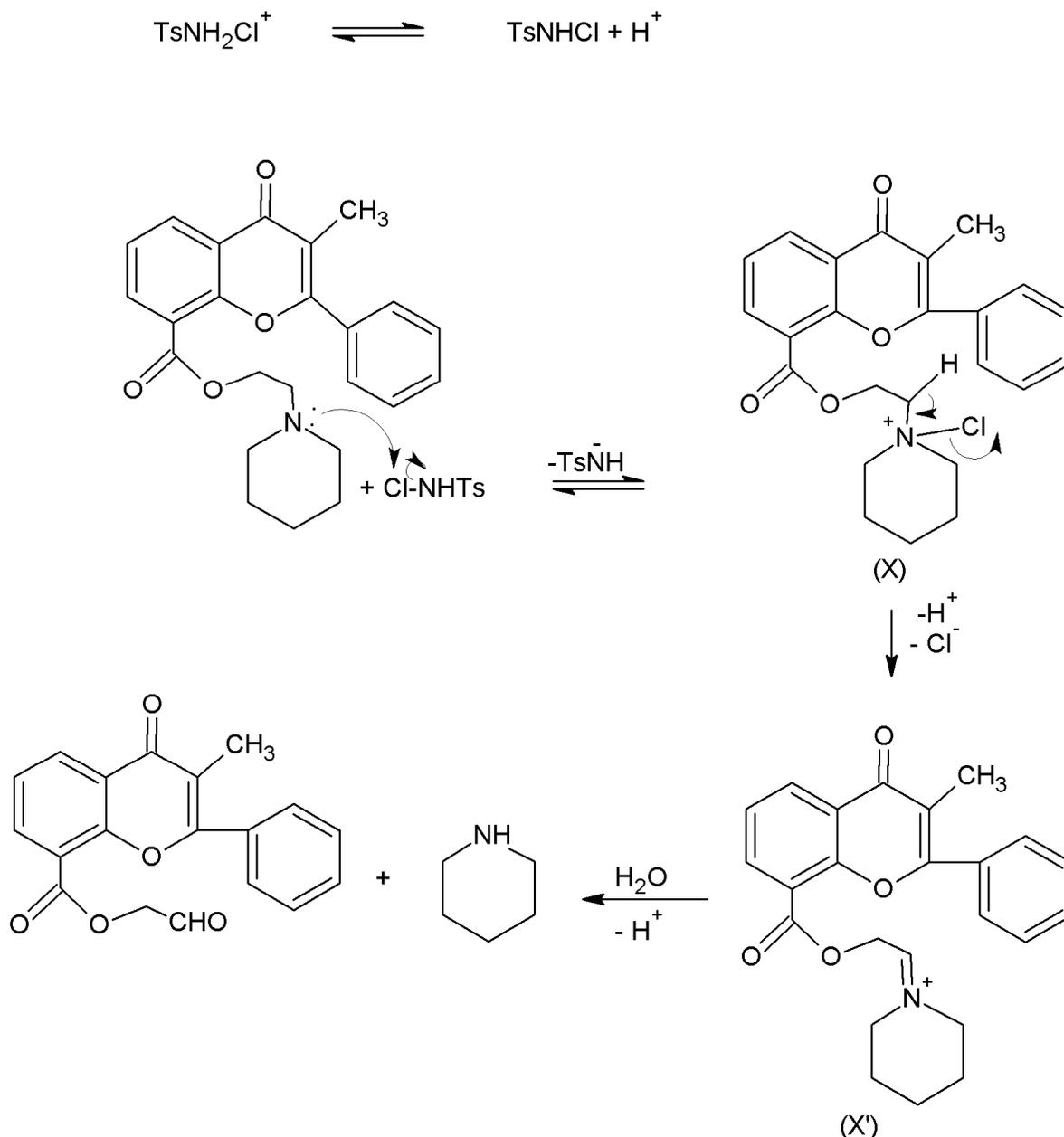
$$TsNHCl + H^+ \rightleftharpoons TsNH_2Cl^+ \qquad (7)$$

The second protonation constant for CAT is $102 \pm 5M^{-1}$ at 298K. In the present investigations, the negative fractional order in [H$^+$] indicates that the deprotonation of TsNH$_2$Cl$^+$ results in the formation of TsNHCl, which is likely to be the active oxidizing species involved in the mechanism of oxidation of FX.

In scheme 1, FX represents the substrate, X and X$^/$ are the intermediate species. An initial equilibrium involves the formation of an active oxidizing species of the oxidant. In the next step, TsNHCl attacks the substrate to form a complex (X). This complex decomposes in a rate limiting step forming complex cation (X$^/$), with the elimination of TsNH$_2$. In the final step, the intermediate complex (X$^/$) hydrolyses to give the end products. The structures of the complex intermediate species are shown in scheme 2, where a detailed plausible mechanism of oxidation of FX with CAT in HCl medium is illustrated.

$$TsNH_2Cl^+ \underset{}{\overset{K_1}{\rightleftharpoons}} TsNHCl + H^+ \quad \text{(i) fast}$$

$$TsNHCl + FX \underset{}{\overset{K_2}{\rightleftharpoons}} X \qquad \text{(ii) fast}$$

$$X \overset{k_3}{\longrightarrow} X^/ \qquad \text{(iii) slow \& rate limiting step}$$

$$X^/ \overset{k_4}{\longrightarrow} products \qquad \text{(iv) fast}$$

Scheme-1

$$TsNH_2Cl^+ \rightleftharpoons TsNHCl + H^+$$

Scheme-2
Mechanism of Oxidation of [FX] with [CAT]

If the total effective concentration of CAT is $[CAT]_t$, then

$$[CAT]_t = [TsNH_2Cl^+] + [TsNHCl] + [X] \qquad (8)$$

By substituting $[TsNH_2Cl^+]$ and $[TsNHCl]$ from equilibrium steps (i) and (ii) of Scheme 1 in equation 8, one obtains :

$$[X] = \frac{K_1 K_2 [CAT]_t [FX]}{[H^+] + K_1 + K_1 K_2 [FX]} \qquad (9)$$

From the slow step of Scheme 1,

$$Rate = k_3 [X] \qquad (10)$$

By substituting for [X] from equation 9 into equation 10, the following rate law is obtained,

$$Rate = \frac{K_1 K_2 k_3 [CAT]_t [FX]}{[H^+] + K_1 + K_1 K_2 [FX]} \qquad (11)$$

The above rate law is in good agreement with the experimental results, wherein a first order dependence of rate on $[CAT]_0$, fractional order on $[FX]_0$ and an inverse fractional order on $[H^+]$ was observed. Since, rate = $k^{/} [CAT]_0$, rate law can be transformed into equations 12 and 13.

$$k^{/} = \frac{K_1 K_2 k_3 [FX]}{[H^+] + K_1 + K_1 K_2 [FX]} \qquad (12)$$

$$1/k^{/} = \frac{[H^+]}{K_1 K_2 k_3 [FX]} + \frac{1}{K_2 k_3 [FX]} + \frac{1}{k_3} \qquad (13)$$

Based on equation 13, plot of $1/k^{/}$ versus $1/[FX]$ at constant $[H^+]$ and temperature has been found to be linear as seen in figure- 4. From the slopes and intercepts of these plots, values of K_1, K_2 and k_3 were calculated. The decomposition constant k_3 was found to be $8.55 \times 10^{-4} s^{-1}$.
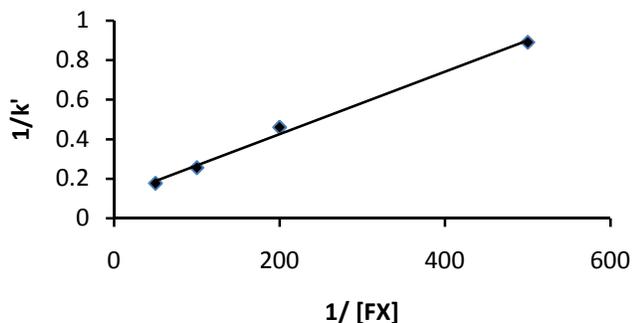

Figure-4
Double reciprocal plot of 1/[FX] versus $1/k^{/}$

The effect of $[FX]_0$ on the rate at different temperatures (293-323K) were examined. From the plots of $1/k^{/}$ versus $1/[substrate]$, values of decomposition constants k_3 were calculated at different temperatures. The activation parameters for the rate limiting step were computed using the Arrhenius plot of log k_3 versus $1/T$. Table 3 summarises the activation parameters.

Addition of halide ions had no effect on the rate indicating that no interhalogen compound or free halogen was formed. The reduction product of oxidant PTS does not influence the rate showing that it is not involved in a pre-equilibrium. The change in the ionic strength of medium does not alter the rate indicating that non-ionic species are involved in the rate limiting step.

The effect of varying solvent composition on the reaction kinetics has been described in several publications for the limiting case of zero angle of approach between two dipoles or an ion-dipole system[19,20]. A plot of log $k^{/}$ versus $1/D$ gave a straight line with a negative slope for a reaction between a negative ion and a dipole or between two dipoles, while a positive slope indicates a reaction between a positive ion and a dipole[20]. The negative dielectric effect observed in the present studies clearly supports the ion-dipole interaction in the rate limiting step.

The proposed mechanism is supported by the observed activation parameters. The moderate values of energy of activation support the proposed mechanism while low values of entropy of activation indicate the formation of rigid associative transition states.

Conclusion

Oxidation of FX by CAT in HCl medium has been studied at 303K. The stoichiometry of the reaction was found to be 1:1. Oxidation products have been characterised. $CH_3C_6H_5SO_2NHCl$ was found to be the reactive oxidizing species. Thermodynamic parameters were computed from the Arrhenius plot. The observed results have been explained by a plausible mechanism and the related rate equation has been deduced.

Acknowledgement

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