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Kinetics of oxidation of Gabapentin by Bromamine-B in NaOH medium- A Mechanistic Approach

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ABSTRACT

The oxidation of gabapentin (GP) with sodium N-bromobenzenesulphonamide (BAB) in NaOH medium has been kinetically investigated at 303K. The reaction rate exhibits a first-order kinetics with respect to [BAB] and fractional-order in both $[GP]_0$ and [NaOH].Variation of ionic strength of the medium, addition of halide ions and reduction product benzenesulphonamide have no significant effect on the reaction rate. The rate of the reaction increases with increase in dielectric constant of the reaction medium. Activation parameters have been computed based on Arrhenius plots. The stoichiometry of the reaction was found to be 1:2 and main oxidation products were identified. Michaelis-Menten type of kinetics has been proposed. $C_6H_5SO_2NBr^-$ has been assumed to be the reactive oxidizing species.The proposed mechanism and derived rate equation are consistent with the observed kinetic data.

Keywords: Kinetics **,** Oxidation, Bromamine-B, Gabapentin

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INTRODUCTION

N-haloamines are mild oxidants and generally undergo a two electron change per mole in its reactions.They act as sources of halonium cations,hypohalite species and N-anions,which act both as bases and nucleophiles[1]. There are many reports on N-halocompounds behaving as oxidizing agents. However ,a review of literature shows that although the reaction of aromatic sulphonylchloramines have been known and extensively investigated [2,3],there is not much of information available [4,5] on the reaction of corresponding bromamines, bromamine-T and bromamine-B. Sodium N-bromobenzenesulphonamide or bromamine-B ($C_6H_5SO_2NBrNa$ 1.5 H_2O or BAB) has gained importance as a mild oxidant and it can be readily prepared by brominating CAB. Bromamine-B is found to be a most potential oxidant among these N-haloamines. However, little information exists in the literature[6,7] on BAB reactions particularly with respect to the kinetics and mechanistic aspects of oxidation of pharmaceuticals. For these reasons, it was felt interesting to investigate the mechanism of oxidation of gabapentin by BAB.

Gabapentin is an anti-epileptic and anti-convulsant drug[8,9] .It is prescribed for prevention of seizures. It is also used to treat nerve pain caused by herpes virus. The mechanisms for the analgesic and anticonvulsant effects of gabapentin are not yet understood well. The present paper reports for the first time a detailed kinetic study of oxidation of gabapentin with BAB in alkaline medium. This kind of study may throw some light on the mechanism of metabolic conversions in the biological system.

MATERIALS AND METHODS

Experimental

Bromamine-B was prepared from chloramine- B[10]. Its purity was checked by iodometry and further characterized by IR, ^1H and ^{13}C NMR spectroscopy. An aqueous solution of BAB was standardized iodometrically and stored in brown bottles to avoid photochemical deterioration.

Gabapentin obtained from 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 of purity. Doubly distilled water was used for all the measurements. A constant ionic strength of the medium was maintained ($\mu = 5.0\times10^{-3}$ $moldm^{-3}$) using concentrated solution of $NaClO_4$.

Kinetic measurements

The reactions were carried out under pseudo- first order conditions by keeping an excess of gabapentin over BAB. Solutions containing appropriate amounts of GP, NaOH 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 BAB 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 BAB 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 [BAB] against time. The pseudo first-order rate constants ($k^{/}$) calculated were reproducible within $\pm$4%.

Stoichiometry and product analysis

Reaction mixtures containing varying ratios of BAB and gabapentin were equilibrated in the presence of NaOH (10.0×10^{-3} mol dm^{-3}) at 303K for 24h. Iodometric estimation of unreacted BAB in the reaction mixture showed that one mole of gabapentin was consumed by two moles of oxidant, confirming the following stoichiometry:

$$C_9H_{17}NO_2 + 2RNBrNa + 2H_2O \longrightarrow C_9H_{14}O_4 + NH_3 + 2RNH_2 + 2Na^+ + 2Br^- \quad (1)$$

Where, $R = C_6H_5SO_2$

Benzenesulphonamide, a reduction product of BAB was detected by thin layer chromatography [11], using a mixture of petroleum ether, chloroform and n-butanol (2:2:1 v/v) as solvent and iodine as the detecting agent (R_f = 0.88). Further it was confirmed by its melting point 150-151°C (Reported m.p.= 149-152°C). The oxidation product of gabapentin, l-carboxy cyclohexane-1-acetic acid was detected by spot tests and IR studies [12].The bands at1760 cm^{-1} and 1710 cm^{-1} corresponds to two -C=O group and 3550cm^{-1} and 3520cm^{-1} for two –OH group, clearly confirms l-carboxy cyclohexane-1-acetic acid.

RESULTS

Effect of varying reactant concentrations on the reaction rate

Under pseudo-first order conditions, with the substrate in excess, at constant $[GP]_0$, [NaOH] and temperature, plots of $\log[BAB]_0$ versus time were linear indicating a first order dependence of the reaction rate on $[BAB]_0$. Values of pseudo-first order rate constants ($k^{/}$) are given in Table 1. Further, these values are unaffected by a variation of $[BAB]_0$ confirming the first order dependence on $[oxidant]_0$.Under similar experimental conditions, an increase in $[GP]_0$ increased the $k^{/}$ values (Table1). A plot of log $k^{/}$ versus log [GP] was linear (Fig 1) with a slope of 0.413, showing a fractional order dependence of the rate on $[GP]_0$.

Effect of NaOH on the reaction rate

The rate of the reaction increased with increase in [NaOH] (Table 1) and a plot of log $k^{/}$ versus $\log[OH^-]$ was linear (Fig 1) with a slope of 0.19 indicating a fractional order dependence of rate on [NaOH].

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Table 1: Effect of varying reactant concentrations on the reaction rate

$10^4[BAB]_0$ (mol dm^{-3})	$10^3[GP]_0$ (mol dm^{-3})	$10^3[NaOH]$ (mol dm^{-3})	$10^4 k'$ (s^{-1})
10.0	1.0	10.0	1.42
10.0	2.0	10.0	2.04
10.0	5.0	10.0	2.84
10.0	10.0	10.0	3.80
10.0	20.0	10.0	5.00
10.0	50.0	10.0	7.40
5.0	10.0	10.0	3.74
10.0	10.0	10.0	3.82
15.0	10.0	10.0	3.78
20.0	10.0	10.0	3.68
10.0	10.0	1.0	1.38
10.0	10.0	5.0	3.20
10.0	10.0	10.0	3.80
10.0	10.0	20.0	4.40
10.0	10.0	50.0	5.00

I=5.0×10^{-3} mol dm^{-3} ; T = 303K

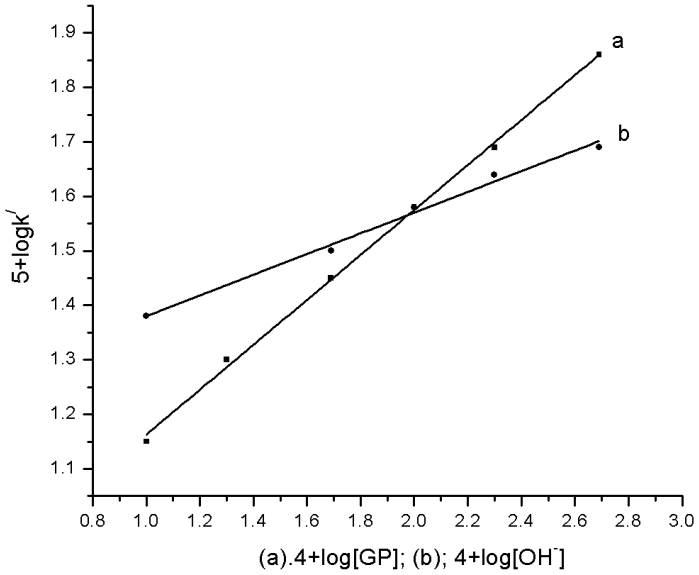

Fig 1. Effect of varying concentrations of gabapentin and NaOH

Effect of varying concentrations of benzenesulphonamide [BSA] on the reaction rate

The addition of reduction product benzenesulphonamide ($1.0x10^{-3}$ to $5.0x10^{-2}$ mol dm^{-3}) to the reaction mixture did not affect the rate significantly, this indicated its non-involvement in a pre-equilibrium with the oxidant.

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Effect of varying concentrations of halide ions on the reaction rate

At constant [OH^-] (10.0×10^{-3}mol dm^{-3}), maintained with NaOH, addition of NaCl and NaBr (1.0×10^{-3}-5.0×10^{-2} mol dm^{-3}) had no significant effect on the rate of the reaction.

Effect of ionic strength and dielectric permittivity of the medium on the reaction rate

The reaction rate remained unaffected upon varying the ionic strength of the reaction medium by addition of $NaClO_4$ (1.0×10^{-3}-5.0×10^{-2}mol dm^{-3}).The dielectric permittivity of the medium was varied by adding different proportions of methanol (0 – 30%, v/v) to the reaction mixture. The rate increased with increase in dielectric permittivity of the reaction mixture (Table 2). A plot of log $k^/$ versus 1/D, (Fig 2) where D is the dielectric permittivity of the medium (D values are taken from the literature [13]) was linear with a positive slope.

Table 2: Effect of dielectric constant of the medium

MeOH %[v/v]	D	$10^4k^/$ (s^{-1})
0.0	76.73	3.80
10.0	72.37	5.01
20.0	67.48	6.76
30.0	62.71	10.00

[BAB] = 10.0×10^{-3}mol dm^{-3}; [GP] = 10.0×10^{-3}mol dm^{-3} ; [NaOH]= 10.0×10^{-3}mol dm^{-3}; I=5.0×10^{-3} mol dm^{-3} ; T=303K

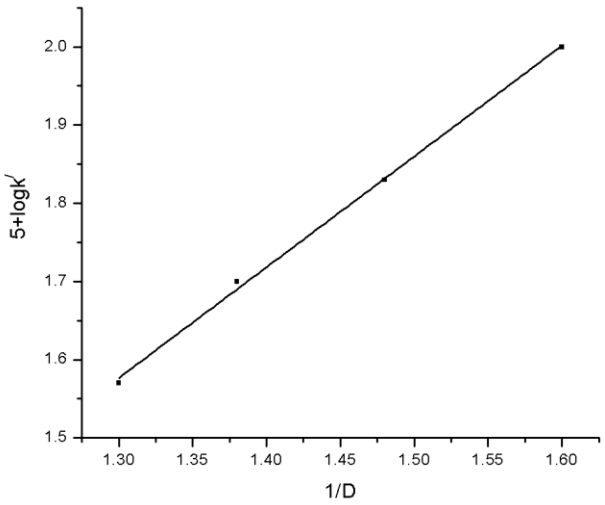

Fig 2. Effect of dielectric constant of the medium

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Effect of varying temperature on the reaction rate

The reaction has been carried out at various temperatures (293- 323 K) keeping other experimental conditions constant (Table 3). From the linear Arrhenius plot of log $k^{/}$ versus 1/T (Fig 3), values of activation parameters have been computed. Table 3 summarizes all these results.

Table 3: Effect of temperature on the reaction rate and activation parameters

Temperature K	$10^4 k^{/}$ (s^{-1})	$10^4 k_3$ (s^{-1})	Activation Parameters
293	2.50	(3.33)	Ea , $kJmol^{-1}$ 33.23 (48.36)
303	3.80	(6.60)	$\Delta H^{\#}$, $kJmol^{-1}$ 30.71 (45.84)
313	5.60	(12.5)	$\Delta S^{\#}$, $JK^{-1}mol^{-1}$ -209.6 (-155.3)
323	8.30	(25.0)	$\Delta G^{\#}$, $kJmol^{-1}$ 94.21 (92.89)

Note: Values in parenthesis are the decomposition constants and activation parameters for the rate limiting step.

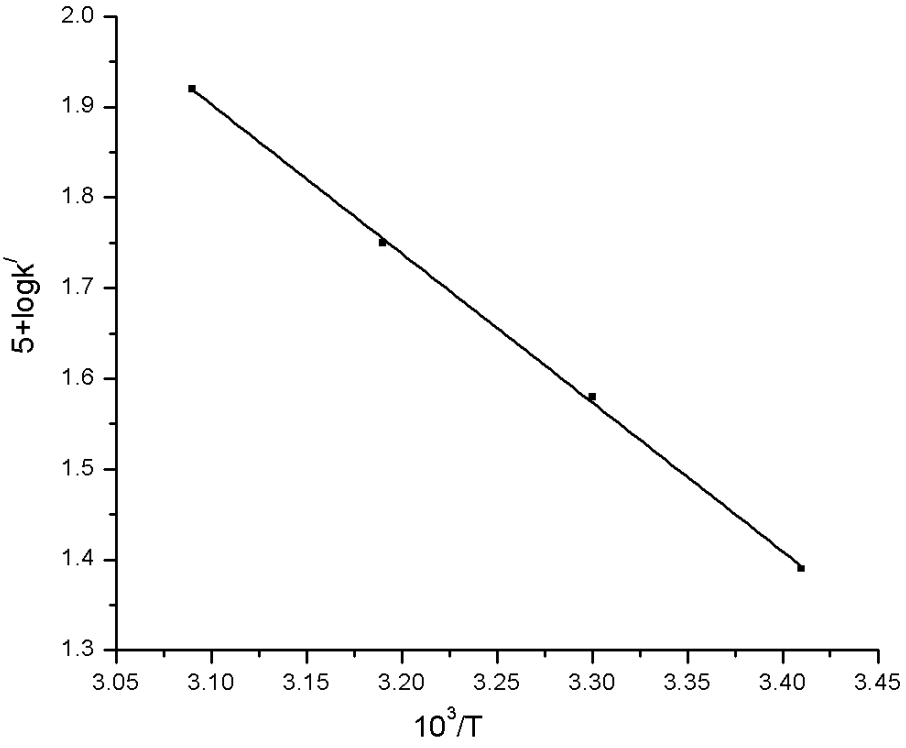

Fig. 3 Effect of temperature on the reaction rate

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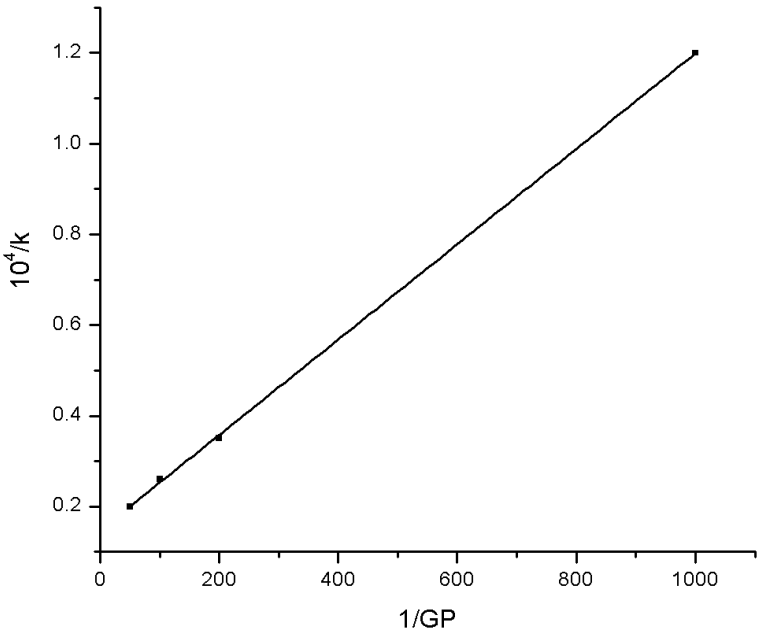

Fig.4 Plot of 10^4 / $k^{/}$ versus 1/[GP]

Test for the free radicals

Addition of the reaction mixture to aqueous acrylamide solution did not initiate polymerization which indicates the absence of free radicals species.

DISCUSSION

Organic haloamines have similar chemical properties and hence it is expected that similar equilibria would exist in solutions of these compounds[14-16]. Bromamine-B which is analogous to chloramine-T and chloramine-B behaves like a strong electrolyte both in acidic and alkaline media[17]. In alkaline solutions of bromamines and dibromamines, $TsNBr_2$ does not exist. The possible oxidizing species are RNHBr , $RNBr^-$ and OBr^- which could be transferred into more reactive oxidizing species HOBr during the course of the reaction in alkaline medium. Hardy and Johnston[17] have reported the existence of following equilibria in alkaline solution of BAB

$$RNBr^- + H_2O \rightleftharpoons RNHBr + OH^- \quad (2)$$

$$RNHBr + H_2O \rightleftharpoons RNH_2 + HOBr \quad (3)$$

As equation(3) indicates, if HOBr is the primary oxidizing species, first order retardation of the rate by the added benzenesulphonamide would be expected. However, no such effect was observed. If RNHBr were the reactive species, a retardation of the rate by $[OH^-]$ would be expected according to equation(2), which is contrary to the experimental observations. Therefore it is likely that the anion $RNBr^-$ is the probable oxidizing species for the oxidation of GP by BAB in alkaline medium. The following mechanism (Scheme 1) is proposed to account for the observed kinetics:

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$$RNHBr + OH^- \underset{}{\overset{K_1}{\rightleftharpoons}} RNBr^- + H_2O \qquad \text{(i) fast}$$

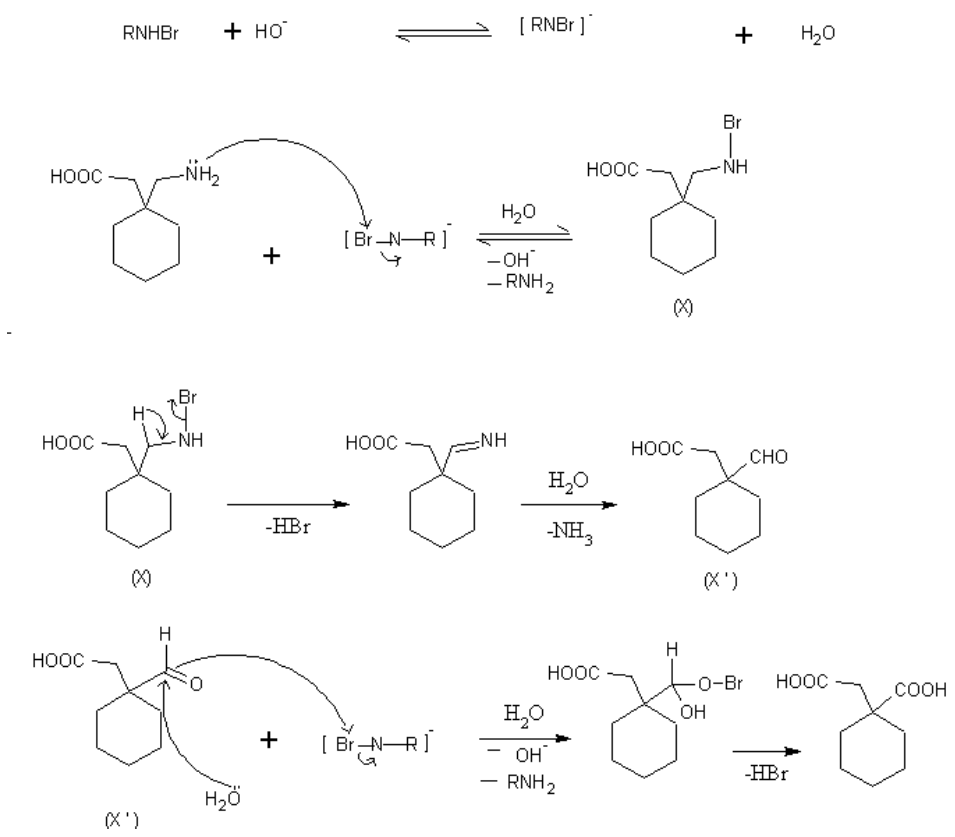
$$RNBr^- + GP \underset{}{\overset{K_2}{\rightleftharpoons}} X \qquad \text{(ii) fast}$$

$$X \xrightarrow{k_3} X' \qquad \text{(iii) slow \& rds}$$

$$RNBr^- + X' \xrightarrow{k_4} \text{Products} \qquad \text{(iv) fast}$$

Scheme 1

In scheme 1, GP represents the substrate, X and X/ represents the complex intermediate species whose structures are shown in scheme 2, where a detailed mechanism of oxidation of GP with BAB in NaOH medium is illustrated. An initial equilibrium involves formation of active oxidizing species $RNBr^-$. In the next step, the anion attacks the nitrogen atom of the substrate which results in the formation of complex X with the elimination of RNH_2. The complex X undergoes rearrangement to form intermediate complex X/ with the elimination of a molecule of ammonia. In the final step , this complex reacts with one more molecule of the anion to form the products.



Scheme 2

From the slow step of scheme 1,

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$$\text{Rate} = k_3 [X] \quad (4)$$

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

$$[BAB]_t = [RNHBr] + [RNBr^-] + [X] \quad (5)$$

By substituting [RNHBr] and $[RNBr^-]$ from steps (i) and (ii) of Scheme 1 in equation(5) one obtains,

$$[X] = \frac{K_1 K_2 [BAB]_t [GP] [OH^-]}{[H_2O] + K_1[OH^-] + K_1 K_2 [GP] [OH^-]} \quad (6)$$

By substituting [X] from equation(6) into equation(4),the following rate law is obtained:

$$\text{Rate} = \frac{K_1 K_2 k_3 [BAB]_t [GP] [OH^-]}{[H_2O] + K_1[OH^-] + K_1 K_2 [GP] [OH^-]} \quad (7)$$

The rate equation (7) is in good agreement with the experimental results.
Since rate = $k^/ [BAB]_t$, equation(7) can be transformed into equations (8)-(9)

$$k^/ = \frac{K_1 K_2 k_3 [GP] [OH^-]}{[H_2O] + K_1[OH^-] + K_1 K_2 [GP] [OH^-]} \quad (8)$$

$$1/k^/ = \frac{1}{K_2 k_3 [GP]} \left\{ \frac{[H_2O]}{K_1 [OH^-]} + 1 \right\} \frac{1}{k_3} \quad (9)$$

From the slopes and intercepts of plots of $1/k^/$versus1/[GP] (Fig 4) and 1/k'vs1/$[OH^-]$ values of K_1,K_2 and k_3 were calculated and found to be 3.7×10^{-1}moldm^{-3} 531.9 dm^{3}mol^{-1} and 6.6×10^{-4} s^{-1} respectively.

The positive dielectric effect in the present case supports the involvement of ion –dipole interaction in the rate limiting step. Addition of halide ions had no effect on the rate , indicating that no interhalogen or free bromine was formed. Benzenesulphonamide does not influence the rate, showing that it is not involved in a pre-equilibrium. Variation of ionic strength of the medium does not alter the rate, indicating non-ionic species are involved in the rate limiting step. The proposed mechanism is also supported by the moderate values of energy of activation and other thermodynamic parameters (Table 3).The partly high positive values of $\Delta H^{\#}$ and $\Delta G^{\#}$ indicates that the transition state is highly solvated, while the negative value of $\Delta S^{\#}$ suggests that the transition state is fairly rigid with less degree of freedom.

CONCLUSIONS

Oxidation of gabapentin with bromamine-B in alkaline medium has been kinetically studied. The stoichiometry of the reaction was found to be 1:2. The oxidation product of GP was identified as l-carboxy cyclohexane-1-acetic acid. and $C_6H_5SO_2NBr^-$ was found to be the

reactive oxidizing species. Activation 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.

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