React. Kinet. Catal. Lett., Vol. 18, No. 3–4, 415–420 (1981)

# KINETICS AND MECHANISM OF OXIDATION OF SULFAGUANIDINE BY PEROXYDISULFATE ION

S. P. Srivastava, A. K. Mittal and V. K. Gupta

Department of Chemistry, University of Roorkee, Roorkee–247672, India

Received April 23, 1981
Accepted July 16, 1981

Results of the kinetic studies of peroxydisulfate ion oxidation of sulfaguanidine are discussed. N,N'-bis(guanyl)azoxybenzene-p,p'-disulfonamide has been identified as the main oxidation product. On the basis of product identification and kinetic studies a radical mechanism is proposed.

Обсуждаются результаты кинетических исследований окисления сульфагуанидина с помощью иона пероксидисульфата. N,N'-Бис (гуанил) азоксибензол-п,п'-дисульфонамид был идентифицирован как основной продукт реакции. На основе идентифицированного продукта, а также кинетических данных предлагается радикальный механизм реакции.

## INTRODUCTION

In our earlier communication /1/ we have reported the oxidation of sulfasomidine by peroxydisulfate ion. The present paper contains our findings on the oxidation of sulfaguanidine ((N-guanyl)-4-aminobenzenesulfonamide) by peroxydisulfate ion.

## EXPERIMENTAL

Potassium peroxydisulfate (Riedel, A. G.) and sulfaguanidine IP (CIBA-GEIGY) were used after recrystallization. All other chemicals used were of analytical grade. Solution of sulfaguanidine was prepared in 0.066 N $H_2SO_4$.

The progress of the reaction was followed by the same method as in the previous study /1/.

## RESULTS AND DISCUSSION

N,N'-bis(guanyl)azoxybenzene-p,p'-disulfonamide was identified as the main oxidation product by its IR, UV, elemental analysis and group tests. The stoichiometry of the reaction for the early stage was 1 mol of sulfaguanidine per 1 mol of per-

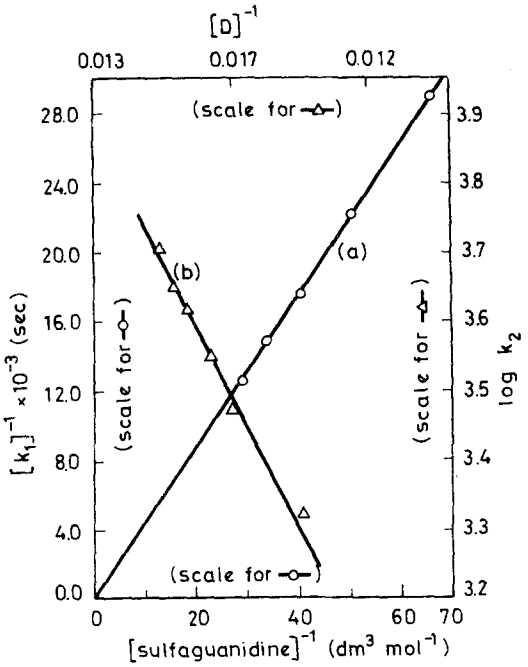



Fig. 1. (Curve a): Dependence of reciprocal first order rate constant on reciprocal sulfaguanidine concentration, temp. 45 °C. $[K_2S_2O_8] = 2.0 \times 10^{-3}$ mol dm$^{-3}$
(Curve b): Amis plot for dielectric constant dependence, temp. 45 °C. $[K_2S_2O_8] = 1.0 \times 10^{-2}$ mol dm$^{-3}$; [Sulfaguanidine] = $1.0 \times 10^{-2}$

Table 1

Kinetic data at different substrate and oxidant concentrations (45 °C)

| $[K_2S_2O_8] \times 10^2$ (mol dm$^{-3}$) | $[K_2SO_4] \times 10^2$ (mol dm$^{-3}$) | [Sulfaguanidine] $\times 10^2$ (mol dm$^{-3}$) | $k_2 \times 10^3$ (mol$^{-1}$ dm$^3$ s$^{-1}$) |
|---|---|---|---|
| 1.0 | 3.0 | 1.5 | 3.65 |
| 1.5 | 2.0 | 1.5 | 3.61 |
| 2.0 | 2.0 | 1.5 | 3.60 |
| 2.5 | 1.5 | 1.5 | 3.60 |
| 2.0 | 0.0 | 1.0 | 2.46 |
| 2.0 | 0.0 | 1.5 | 2.44 |
| 2.0 | 0.0 | 2.0 | 2.39 |
| 2.0 | 0.0 | 2.5 | 2.43 |

Table 2

Effect of ionic strength $[K_2S_2O_8] = 1.0 \times 10^{-2}$ mol dm$^{-3}$; [sulfaguanidine] $= 1.0 \times 10^{-2}$ mol dm$^{-3}$ Temp. = 45 °C

| $[K_2SO_4] \times 10^2$ (mol dm$^{-3}$) | 0.0 | 1.0 | 2.5 | 5.0 | 7.5 |
|---|---|---|---|---|---|
| Ionic strength ($\mu$) | 0.03 | 0.06 | 0.105 | 0.18 | 0.25 |
| $k_2 \times 10^3$ (mol$^{-1}$ dm$^3$ s$^{-1}$) | 3.42 | 3.68 | 4.08 | 4.81 | 5.64 |

oxydisulfate. The data in Table 1 show that the reaction is of second order, being first order in each reactant, as found by the application of van't Hoff's differential method. The ionic strength was kept constant when the variation of $S_2O_8^{2-}$ was made.

A plot of $\frac{1}{k_1}$ vs. $\frac{1}{[S]}$ (Fig. 1, curve a) (under pseudo-first order conditions, where S is the concentration of the substrate and $k_1$ is the pseudo-first order rate constant) at high substrate concentration was found to be linear, the line passing through the origin. This further confirms the second order kinetic behavior and indicates that no stable complex between substrate and oxidant is formed /2, 3/. The reciprocal of the slope of this curve gave a value of $2.27 \times 10^{-3}$ mol$^{-1}$ dm$^3$ s$^{-1}$ for the second order rate constant, which is in good agreement with the values in Table 1. The reaction was studied at six different temperatures between 303 and 328 K. The reaction obeys the Arrhenius equation, as a plot of log $k_2$ vs. $\frac{1}{T}$ was found to be linear. The various activation parameters thus evaluated are,

$$E_a = (71.4 \pm 0.8 \text{ kJ mol}^{-1}), \quad \Delta H^{\ddagger} = (68.8 \pm 0.8 \text{ kJ mol}^{-1})$$
$$\Delta G^{\ddagger} = (93.7 \pm 1.2 \text{ kJ mol}^{-1}), \quad \Delta S^{\ddagger} = -(79.0 \pm 1.0) \text{ JK}^{-1} \text{ mol}^{-1}$$
$$A = (1.3 \pm 0.1) \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$$

The energy of activation for this reaction is characteristic of second order reactions in solution, suggesting that the initial step does not involve the dissociation of $S_2O_8^{2-}$ into two $\dot{SO}_4^-$, which requires rather more energy /4/ (110–112 kJ mol$^{-1}$).

Reaction rate was found to increase slightly with an increase in ionic strength (maintained by adding $K_2SO_4$) (Table 2). A plot of log $k_2$ vs. $\mu$ was found to be linear (primary kinetic salt effect), thereby indicating that the reaction might be taking place between an ion and a neutral molecule. The rate of the reaction was found to decrease with decreasing dielectric constant of the medium. A plot of log $k_2$ vs. 1/D (Fig. 1, curve b) was found to be linear with a negative slope, suggesting that the reacting species may be an anion and a neutral molecule /6/. This also accounts for the large negative entropy of activation observed. DPPH

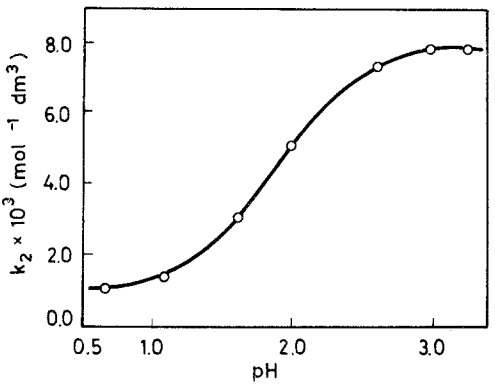



Fig. 2. Effect of pH on the rate constant (temp. 45 °C). $[K_2S_2O_8] = 1.0 \times 10^{-2}$ mol dm$^{-3}$; [Sulfaguanidine] $= 1.0 \times 10^{-2}$ mol dm$^{-3}$

Table 3

Effect of DPPH $[K_2S_2O_8] = 1.0 \times 10^{-2}$ mol dm$^{-3}$; [sulfaguanidine] $= 1.0 \times 10^{-2}$ mol dm$^{-3}$ Temp. = 45 °C

| [DPPH] x $10^4$ (mol dm$^{-3}$) | 0.0 | 1.0 | 2.0 | 3.0 |
|---|---|---|---|---|
| $k_2$ x $10^3$ (mol$^{-1}$ dm$^3$ s$^{-1}$) | 3.42 | 3.19 | 2.83 | 2.0 |

(diphenylpicrylhydrazyl) inhibited the rate appreciably (Table 3), indicating the radical nature of the reaction.

The pH rate profile (Fig. 2) indicates that the rate increases sharply from pH 0.65 to 3.00 after which it becomes nearly independent of pH. This pH dependence suggests that it is the unprotonated sulfaguanidine molecule which is attacked by peroxydisulfate ion. Further, it can be inferred that the protonation of sulphaguanidine above pH 3.00 is rather negligible. Similar pH dependence was observed in case of sulfasomidine oxidation /1/.

## MECHANISM

On the basis of kinetic and other evidence embodied in this paper and taking into account the similar kinetic behavior of this reaction to that of sulfasomidine oxidation, a general mechanism is suggested for the oxidation of sulfa drugs on the

example of sulfaguanidine

$$RNH_2 + S_2O_8^{2-} \xrightarrow{k^I} \dot{R}\dot{N}H + HSO_4^- + SO_4^{\cdot-}$$

$$SO_4^{\cdot-} + RNH_2 \xrightarrow{k^{II}} \dot{R}\dot{N}H + HSO_4^-$$

$$R\text{–}\dot{N}H + R\text{–}\dot{N}H \xrightarrow{k^{III}} R\text{–}NH\text{–}NH\text{–}R$$

$$RNHNHR + S_2O_8^{2-} \xrightarrow{k^{IV}} R\text{–}N{=}N\text{–}R + 2HSO_4^-$$

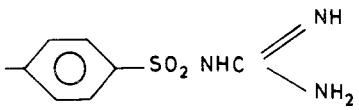
azo compound

$$R\text{–}N{=}N\text{–}R + S_2O_8^{2-} + H_2O \xrightarrow{k^V}$$

$$\longrightarrow \quad R\text{–}\overset{\overset{O}{\uparrow}}{N}{=}N\text{–}R + 2HSO_4^-$$

azoxy compound

In the above equations $RNH_2$ stands for




Thus the proposed mechanism assumes a direct bimolecular reaction between $S_2O_8^{2-}$ and $NH_2$ group of the drug, resulting in hydrogen abstraction, which is followed by coupling of $2\dot{R}\dot{N}H$ radicals leading to the formation of hydrazo compound which on oxidation gives azo compound, and the azo-compound can be further oxidized to azoxy-compound.

Applying the steady state treatment to radicals $\dot{R}\dot{N}H$, $SO_4^{\cdot-}$, the following rate law is obtained

$$\frac{-d[S_2O_8^{2-}]}{dt} = k_2\,[RNH_2]\,[S_2O_8^{2-}]$$

where $k_2 = 3k^I$ is the experimental second order rate constant.

The proposed mechanism is in conformity with the various kinetic features observed, namely the second order behavior, primary linear salt effect, pH effect, effect of dielectric constant and inhibition by DPPH.

*Acknowledgement.* One of us (VKG) is highly thankful to CSIR, New Delhi, India for awarding a post-doctoral fellowship.

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