A Kinetic Study of Peroxydisulphate Oxidation of Sulphadrugs—Oxidation of Sulphanilamide

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The peroxydisulphate oxidation of sulphanilamide follows second order kinetics being first order in each of the reactants. However, the Ag+-catalysed oxidation is found to be composed of two simultaneous reactions — a first order Ag+-catalysed reaction and a second order uncatalysed reaction. p,p'-Azoxybenzene disulphonamide has been identified as the oxidation product. The reaction is insensitive to ionic strength variation. Energy parameters have been evaluated. A possible radical mechanism is suggested and rate law derived therefrom.

SULPHADRUGS, undergo oxidation in the human metabolism and result in the formation of different oxidation products which may be responsible for the possible side effects observed. It has earlier been postulated by Mayer et al.[1] that the oxidation products of sulphonamides exert bacteriostatic action. Polarographic studies on sulphonamides have been reported by Kolthoff et al.[2]. With a view to getting insight into the possible modes of oxidation of different sulphadrugs, kinetic study of oxidation of sulphanilamide by peroxydisulphate ion has now been carried out and the results are reported in this paper.

Materials and Methods

$K_2S_2O_8$ (AR, Riedel) and sulphanilamide (IDPL) were used after recrystallization and drying under vacuum. All other chemicals used were of analytical grade.

The progress of the reaction was followed by estimating the unreacted $K_2S_2O_8$ at different intervals of time iodometrically by the method of Szabo et al.[3], as modified by Khulbe and Srivastava[4]. Kinetic runs were made in iodine flasks of Corning glass maintained at the desired temperature with an accuracy of ±0·1°. No appreciable change in rate was observed when the reaction was carried out in dark. Hence all kinetic studies were made in diffused light.

Results and Discussion

Order of reaction — The uncatalysed reaction shows second order kinetics, being first order each in oxidant and substrate. This was found out by applying van't Hoff's differential method for different kinetic runs at different concentrations of one or the other reactant. This was further confirmed by carrying out kinetic runs at different high concentrations of substrate and at constant low concentration of $K_2S_2O_8$ when the reaction was found to follow pseudo-first order kinetics. The plot of $1/k$ versus $1/[S]$ was linear passing through the origin, thereby confirming the first order dependence in

substrate and indicating that no complex between sulphanilamide and $S_2O_8^{2-}$ is formed in a slow process.

Effect of using different catalysts — Cu(II) ion has no appreciable catalytic effect but the reaction is catalysed by Ag+ ion. In the presence of Ag+ ion, the reaction rate is found to obey the following relationship:

$$(-dc/dt) = k_0[Ag^+][S_2O_8^{2-}] + k_2[S_2O_8^{2-}][S] \quad \ldots(1)$$
$$= k_1[S_2O_8^{2-}] + k_2[S_2O_8^{2-}][S] \quad \ldots(2)$$

Equation (2) can be put in the form:

$$k = \frac{(-dc/dt)}{[S_2O_8^{2-}]} = k_1 + k_2[S] \quad \ldots(3)$$

where $k_1 (= k_0[Ag^+])$ is the first order rate constant for the Ag+-catalysed reaction and k_2 is the second order rate constant for the uncatalysed reaction. Equation (3) was verified in the following manner:

The value of k was evaluated by determining $(-dc/dt)$ for the catalysed reaction and dividing it by the concentration of $S_2O_8^{2-}$ employed. k_2 was evaluated by independent kinetic runs for the uncatalysed reaction at the same concentrations of $S_2O_8^{2-}$ and substrate as empoyed for the Ag+-catalysed reaction. Then k_1 was calculated with the help of Eq. (3), which should be constant for a particular concentration of Ag+, and this has been found to be true as shown by the data of Table 1.

This relationship was further verified by varying the concentration of $AgNO_3$, keeping concentrations of the other reactants constant and then calculating the value of k_1 in each case in the same manner as above and thereby evaluating k_0 from the relationship $k_0 = k_1/[Ag^+]$. This value of k_0 is found to be nearly constant (Table 2) and is the same as in the previous runs.

Thus it can safely be concluded that the Ag+-catalysed reaction is composed of two simultaneous reactions — a first order Ag+-catalysed reaction and a second order uncatalysed reaction.

TABLE 1 — EFFECT OF VARYING [REACTANT] ON THE
REACTION RATE IN THE Ag^+-CATALYSED AND
UNCATALYSED OXIDATION OF SULPHANILAMIDE BY
PEROXYDISULPHATE

(Temp. = $40° \pm 0.1°$)

$[S] \times 10^2 M$	$[K_2S_2O_8] \times 10^2 M$	$k_2 \times 10^3$ lit mole^{-1} sec^{-1}	$k_1 \times 10^5$* sec^{-1}
1·00	1·0	5·4	3·15
1·25	1·0	5·2	3·75
1·25	2·0	5·0	3·55
1·50	2·0	5·0	3·07
2·00	1·0	5·0	3·88
2·00	1·5	5·0	3·40
2·00	2·0	5·0	3·20
2·50	1·0	5·1	3·50

*In the presence of $5.0 \times 10^{-4} M$ $AgNO_3$.

TABLE 2 — EFFECT OF VARYING [$AgNO_3$] CONCENTRATION
ON THE REACTION RATE

{$[S] = 1.0 \times 10^{-2} M$; $[K_2S_2O_8] = 1.0 \times 10^{-2} M$; temp.$= 40° \pm 0.1°$}

$[AgNO_3] \times 10^3 M$	0·50	0·75	1·00	1·25	1·50	1·75
$k_1 \times 10^5$ sec^{-1}	3·15	4·54	6·18	7·55	8·76	10·00
$k_0 \times 10^2$ litre mol^{-1} sec^{-1}	6·30	6·05	6·18	6·04	5·84	5·70

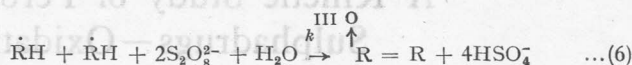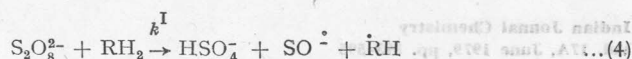*Stoichiometry* — One mol of substrate is found to consume 1·5 mols of $K_2S_2O_8$ when reaction mixture is allowed to stand at 55°.

Product analysis — Aqueous solutions of sulphanilamide (0·029M) and potassium peroxydisulphate (0·087M) were mixed and kept at 80° in a water-bath for 2 hr. The precipitated product was filtered off after further allowing the reaction mixture to stand at room temperature for 24 hr (yield 40%). The product was purified by repeated crystallizations from DMF-water mixture. The product decomposed above 300°.

The product showed the functional group test for azo or azoxy and for sulphonamido groups. However, on the basis of UV and IR spectral studies, the product was characterized as p,p'-azoxybenzenedisulphonamide; [λ_{max} (in ethanol) at 219, 231 and 327 nm and absence of absorption peak in the 440-470 nm region]; [ν_{max} 3255, 3345 (νNH of SO_2NH$_2$), 1335, 1145 (νSO_2 of SO_2NH_2) and 1448 cm^{-1} (azoxy)].

The same product has been reported by Seikel[5] in the oxidation of sulphamilamide by H_2O_2 in acetic acid medium.

Effect of temperature — Thermodynamic parameters for the uncatalysed reaction were evaluated by carrying out the reaction at six temperatures in the range 30° to 55°. A value of 13·8 kcal mole^{-1} evaluated for $\Delta E^\ddagger$ is characteristic of the second

$$S_2O_8^{2-} + RH_2 \xrightarrow{k^I} HSO_4^- + SO_4^{-\cdot} + \dot{R}H \quad \text{...(4)}$$

$$SO_4^{-\cdot} + RH_2 \xrightarrow{k^{II}} \dot{R}H + HSO_4^- \quad \text{...(5)}$$

$$\dot{R}H + \dot{R}H + 2S_2O_8^{2-} + H_2O \xrightarrow{k^{III}} \overset{O}{\underset{\uparrow}{R}} = R + 4HSO_4^- \quad \text{...(6)}$$

Scheme 1

order reactions in solution. Other parameters at 40° are: $A = 2.1 \times 10^7$ litre mol^{-1} sec^{-1}; $\Delta S^\ddagger = -27.2$ e.u.; $\Delta F^\ddagger = 21.7$ kcal mol^{-1}; $\Delta H^\ddagger = 13.2$ kcal mol^{-1}.

Effect of pH — The pH variation has little effect on the rate of the reaction, Kolthoff buffer (KH_2PO_4+Borax) being employed for varying the pH. This suggests that no protonation step is involved in this oxidation process.

Effect of ionic strength — The effect of ionic strength has been investigated by carrying out kinetic runs in the presence of varying concentrations of K_2SO_4 as well as $KClO_4$. It is found that, unlike other Ag^+-catalysed reactions of peroxydisulphate ion, there is almost no effect of ionic strength on the rate of the uncatalysed reaction. This suggests that the rate-determining process should not involve a reaction between ions and hence the uncatalysed reaction can be supposed to consist of a direct attack of $S_2O_8^{2-}$ on the sulphanilamide moiety instead of the attack of substrate by SO_4^- radical first formed by thermal dissociation of $S_2O_8^{2-}$ as postulated by Bartlett and Cotman[6], since this should result in half-order in $S_2O_8^{2-}$, which has not been observed.

Mechanism of the uncatalysed reaction — As the reaction has been found to be affected by radical scavengers, the participation of free radicals in the reaction mechanism is indicated.

The second order kinetic behaviour of the reaction and the values of energy parameters are consistent with the mechanism shown in Scheme 1.

where RH_2, $\dot{R}H$ and $R=R$ are $NH_2O_2SC_6H_4NH_2$ (p), $NH_2O_2SC_6H_4\dot{N}H(p)$
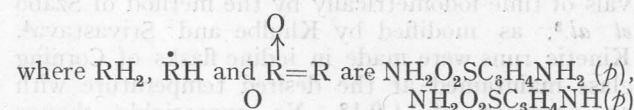
and $NH_2O_2SC_6H_4—N=NC_6H_4SO_2NH_2(p)$ respectively.

Applying steady state treatment to the radicals SO_4^- and $\dot{R}H$ the following rate expression is obtained

$$-\frac{d(S_2O_8^{2-})}{dt} = 3k^I [S_2O_8^{2-}] [RH_2] = k_2 [S_2O_8^{2-}][RH_2] \quad \text{...(7)}$$

where $k_2(= 3k^I)$ is the experimental second order rate constant. However, step (6) should proceed through more than one stage, exact details of which are under investigation.

Acknowledgement

References

1. MAYER, R. L., *Chem. Abstr.*, **33** (1939), 6954; MAYER, R. L. & OECHSLIN, C., *C.r. hebd. Seanc. Acad. Sci.*, **205** (1937), 181.
2. KOLTHOFF, I. M., LEVITAN, N. I., CLARK, W. G. & TENENBERG, D. J., *J. Am. chem. Soc.*, **65** (1943), 2265.
3. SZABO, Z. G., CSANYI, L. & GALIBA, H., *Z. anal. Chem.*, **135** (1952), 269.
4. KHULBE, K. C. & SRIVASTAVA, S. P., *Agra Univ. J. Res. (Sci.)*, **9** (1960), 177.
5. SEIKEL, M. K., *J. Am. chem. Soc.*, **62** (1940), 1214.
6. BARTLETT, P. D. & COTMAN, (Jr), J. D., *J. Am. chem. Soc.*, **71** (1949), 1419.

Some New Approaches to Arrive at the Composition of a very Weak Complex

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