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THERMODYNAMIC AND RELATED STUDIES FOR THE OXIDATION OF SULPHA DRUGS BY THE PEROXYDISULPHATE ION

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ABSTRACT

The results on the studies of various thermodynamic parameters for the oxidation of seven sulpha drugs, viz. sulphanilamide, sulphacetamide(s), sulphasomidine, sulphaguanidine, sulphadiazine, sulphapyridine and sulphamethizole, by the peroxydisulphate ion are reported and discussed. All the reactions under study obeyed the Arrhenius equation. The validity of the isokinetic relationship and other related equations have been tested. An attempt has been made to correlate these findings with the mechanism operative in the oxidation of sulpha drugs by the peroxydisulphate ion.

INTRODUCTION

One of the important studies in deciding the nature of a mechanism for reactions in solution is the study of the effect of temperature on rate and thus to determine various thermodynamic parameters. The isokinetic relationship [1] and Exner's equations [2] have been found useful for deciding whether a similar interaction mechanism is followed for a reaction series. The value of the isokinetic temperature, β, is used for deciding whether the system is entropy-controlled or enthalpy-controlled. Occasionally, differences in the activation energy have been used as evidence of a change in the reaction mechanism. A review of the literature on oxidations by the peroxydisulphate ion [3–6] revealed that no attempt has been made to study the effect of various thermodynamic parameters on the mechanism for the oxidation of sulpha drugs. Sulpha drugs are an important class of compounds, which are the chief medical weapon against many common Gram-positive bacterial diseases [7]. According to Mayer and Oechslin [8], the bacteriostatic action of sulpha drugs is mainly due to their oxidation products. Hence, it is of great interest to study the nature of the mechanism for the oxidation of sulpha drugs by different oxidizing agents. Keeping this end in view, a systematic study of various thermodynamic parameters has been made to understand the nature of the mechanism operative in the

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peroxydisulphate ion oxidation of sulpha drugs. The validity of the isokinetic relationship and other related equations have been tested. The sulpha drugs chosen for these studies were: sulphanilamide, sulphacetamide sodium, sulphasomidine, sulphaguanidine, sulphadiazine, sulphapyridine and sulphamethizole. The results of these studies are presented and discussed in this paper.

EXPERIMENTAL

Potassium peroxydisulphate (Riedel, A.G.) was used after recrystallisation and dried under vacuum. Since solid $K_2S_2O_8$ also undergoes slow decomposition on keeping, it was tested periodically for the presence of SO_4^{2-} and recrystallised whenever found necessary. The sulpha drugs (IDPL, CIBA-GEIGY, May and Baker) were used after several recrystallisations with hot water or appropriate organic solvents. All other chemicals used were of analytical grade.

The progress of these reactions was followed by estimating the unreacted peroxydisulphate iodometrically [9,10]. In the case of sulphanilamide and sulphacetamide(s), the oxidation reactions were carried out in aqueous medium, those of sulphasomidine and sulphaguanidine in dil H_2SO_4 and those for remaining drugs in 0.05 N NaOH medium, as the latter drugs were sparingly soluble in water at ordinary temperatures.

Overall, all these reactions were found to follow second-order kinetics, being first order in peroxydisulphate ion and first order in the sulpha drugs [11–13]. Hence, these reactions were studied at equimolar concentrations of reactants and the second-order rate constants, k_2, were, therefore, evaluated graphically by plotting $1/(a-x)$ vs. t (where a is the initial concentration of peroxydisulphate ion and x is the concentration after time t). The second-order rate constants, k_2, thus evaluated were then utilised to find out various thermodynamic parameters and for other studies.

RESULTS AND DISCUSSION

Thermodynamic parameters

The kinetics of all these oxidation reactions were studied at different temperatures and at equimolar concentration of reactants to evaluate the thermodynamic parameters, viz. activation energy, E_a, frequency factor, A, entropy of activation, $\Delta S^{\neq}$, enthalpy of activation, $\Delta H^{\neq}$, and free energy of activation, $\Delta G^{\neq}$. The second-order rate constants, k_2, evaluated at four different temperatures are recorded in Table 1. The Arrhenius equation,

TABLE 1

Second-order rate constants at different temperatures for sulpha drugs

Sulpha drug	$k_2 \times 10^3$ (dm^3 mole^{-1} s^{-1})			
	303 K	308 K	313 K	318 K
Sulphanilamide	2.38	3.33	4.94	6.59
Sulphacetamide(s)	2.29	3.41	4.83	6.66
Sulphasomidine	2.31	3.33	4.78	6.70
Sulphaguanidine	0.65	1.02	1.56	2.43
Sulphadiazine	3.17	4.28	6.31	8.57
Sulphapyridine	4.15	5.80	8.33	11.66
Sulphamethizole	2.59	3.71	5.30	7.41

relating temperature and specific rate, given by

$$\log k = -\frac{E_a}{2.303RT} + \text{constant} \qquad (1)$$

was found to be followed, since a plot of log k_2 vs. $1/T$ was found to be linear in each case (Fig. 1). The activation energy for these reactions was evaluated from the slopes of these curves. On the basis of these values of the activation energy, the values of the thermodynamic parameters were then

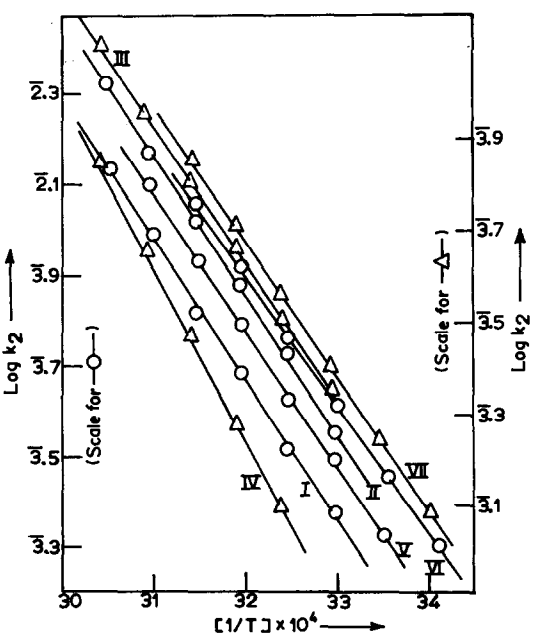


Fig. 1. Arrhenius plots for the oxidation of different sulpha drugs: I, sulphanilamide; II, sulphacetamide(s); III, sulphasomidine; IV, sulphaguanidine; V, sulphadiazine; VI, sulphapyridine; VII, sulphamethizole.

calculated by the application of the equations

$$k = A\, e^{-E_a/RT} \tag{2}$$

$$\Delta S^{*} = 4.576(\log k - 10.753 - \log T) + \frac{E_a}{T} \tag{3}$$

$$\Delta H^{*} = E_a - RT \tag{4}$$

$$\Delta F^{*} = 4.576\, T(\log T + 10.319 - \log k) \tag{5}$$

The thermodynamic parameters thus calculated are given in Table 2. A perusal of the data in this table shows that these reactions are characterised by a large negative value for the entropy of activation, ΔS^{*}. High negative values of ΔS^{*} are mainly observed in less-polar solvents and indicate that solvation effects are predominant in these reactions which suggests the formation of a charged and rigid transition state which is expected to be strongly solvated. Since the present reactions are ion-dipolar type [11–13], it is reasonable to expect that the entropy of the activated complex for all these sulpha drugs should be nearly the same, as was observed in the present studies. However, due to the difference in polarity of the different sulpha drugs and the medium employed, the extent of solvation should be different and hence may cause some variation in the observed ΔS^{*} [14].

A low value for the energy of activation, E_a, observed for these reactions, is characteristic of bimolecular reactions in solution and is of the order of magnitude observed in the case of hydrogen abstraction reactions. This lends support to the postulate made in the proposed mechanism, that the initial step does not involve the dissociation of $S_2O_8^{2-}$ into two $SO_4^{\cdot-}$, as is supposed for some other uncatalysed oxidation reactions of the peroxydisulphate ion [15–19], which requires a much higher energy of activation (110–120 kJ mole^{-1}) [20]. Also, the free energy of activation, ΔG^{*}, and energy of activation, E_a, for all these reactions, are of a comparable order of magnitude, which suggests that the mechanism for all these oxidation

TABLE 2

Thermodynamic parameters for sulpha drugs

Sulpha drug	E_a (kJ mole^{-1})	A (dm^3 mole^{-1} s^{-1})	$-\Delta S^{*}$ (J K^{-1} mole^{-1})	ΔH^{*} (kJ mole^{-1})	ΔF^{*} (kJ mole^{-1})
Sulphanilamide	58.5	2.9×10^{7}	110.4	56.0	90.9
Sulphacetamide(s)	57.3	3.7×10^{7}	108.6	56.6	91.0
Sulphasomidine	58.2	4.2×10^{7}	107.8	56.9	90.5
Sulphaguanidine	72.3	1.3×10^{9}	78.0	68.8	93.7
Sulphadiazine	55.7	1.4×10^{7}	116.6	53.4	89.7
Sulphapyridine	54.7	6.8×10^{6}	122.5	50.9	88.3
Sulphamethizole	56.4	1.8×10^{7}	114.5	54.5	89.5

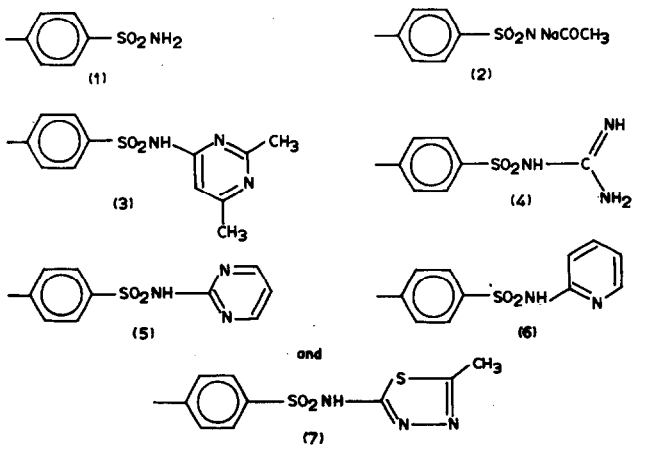


Fig. 2. Groups present at the *para* position in the benzene nucleus of different sulpha drugs. (1) Sulphanilamide; (2) sulphacetamide(s); (3) sulphasomidine; (4) sulphaguanidine; (5) sulphadiazine; (6) sulphapyridine; (7) sulphamethizole.

processes should be similar. The value of frequency factor, A, is of the order of 10^6 to 10^9: this suggests that the reacting species are rather large in size. Furthermore, it can be observed from Table 1 that the rates of oxidation for the different sulpha drugs studied, are of the same order of magnitude in spite of the fact that different moieties (shown in Fig. 2), are present at the amino group of the sulpha drugs. It suggested that the site of attack is only at the nitrogen of the amino group present at the 4-position. A slight variation in rate may be due to a change in the basic strength of different drugs; however, a quantitative relationship between basic strength and rate could not be established because the kinetics for different drugs were carried out employing different solvents.

Validity of the isokinetic relationship and other related equations

The validity of the isokinetic relationship, given by

$$\Delta H^{\neq} = \beta \Delta S^{\neq} \tag{6}$$

(where β is the isokinetic temperature) was tested by plotting a graph of $\Delta S^{\neq}$ vs. $\Delta H^{\neq}$ (Fig. 3), which was found to be linear (correlation coefficient being 0.99), showing thereby that the isokinetic relationship is followed for these reactions. The validity of the isokinetic relationship suggested that the basic mechanism for all these oxidation reactions should be similar. The constancy of the $\Delta G^{\neq}$ values, as reported in Table 1, may be explained on the basis of the isokinetic relationship: for a series of compounds of slightly different structures but undergoing reaction by essentially the same mechanism, the $\Delta G^{\neq}$ values may be more or less constant with relative changes in $\Delta H^{\neq}$ and $\Delta S^{\neq}$, as pointed out by Leffler [1]. The value of the isokinetic

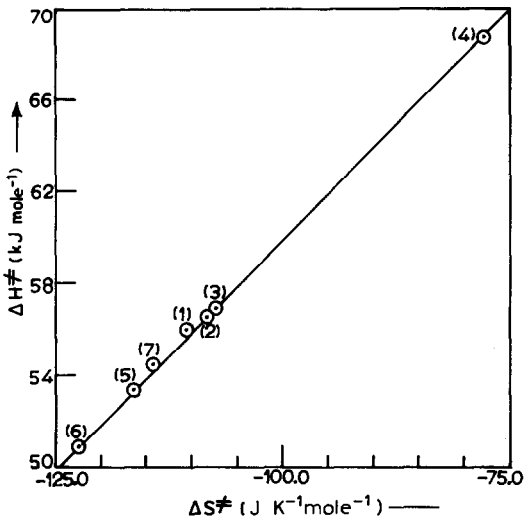


Fig. 3. Isokinetic plot. (1) Sulphanilamide; (2) sulphacetamide(s); (3) sulphasomidine; (4) sulphaguanidine; (5) sulphadiazine; (6) sulphapyridine; (7) sulphamethizole.

temperature, β, given by the slope of the isokinetic plot, came out to be 421 K. Further, Exner [2] has recommended an alternative method for checking and evaluating the value of β, in which the rates of a series of reactions are measured at two temperatures and log k_2 (at T_2) is linearly related to log k_1 (at T_1) according to

$$\log k_2 = a + b \log k_1 \tag{7}$$

The value of the isokinetic temperature, β, can then be calculated from the

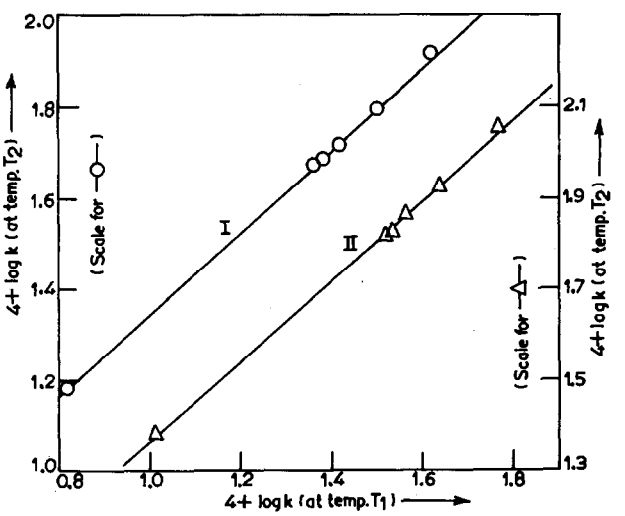


Fig. 4. Exner's plots giving the relationship between log k_2 (at T_2) and log k_1 (at T_1). I, $T_1 = 303$ K, $T_2 = 313$ K; II, $T_1 = 308$ K, $T_2 = 318$ K.

expression

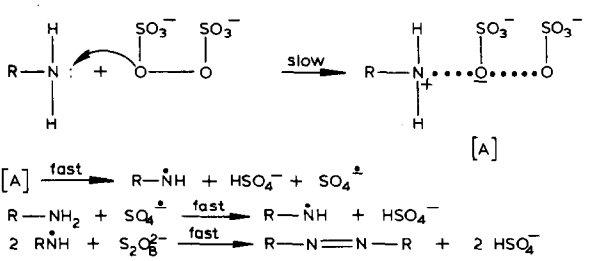
$$\beta = \frac{T_1 T_2 (b-1)}{bT_2 - T_1} \tag{8}$$

In the present studies, plots of log k_2 vs. log k_1 (Fig. 4, curves I and II) were found to be linear, suggesting that Exner's equation, correlating rate constants at two temperatures, is obeyed for these reactions. The value of β calculated by the application of the foregoing equations came out to be 428 K, which is in very good agreement with that evaluated from the isokinetic plot. Thus, the value of β is well above the experimental temperatures employed in the present kinetic studies, suggesting, thereby, that these reactions are enthalpy-controlled [21]. This hypothesis is further supported by the observation that the reaction with the lowest activation energy has the highest rate while that with the highest entropy of activation has the lowest rate.

MECHANISM

Before proposing a mechanism for the reactions under study, it is important to point out here that the rate was greatly decreased by the addition of allylacetate and DPPH to the reaction mixture in the case of each drug and the product of oxidation identified was the corresponding azobenzene derivative. Inhibition of rate by allyl acetate and DPPH suggested the involvement of radicals or radical ions in the mechanism, which is also supported by the low values of activation energy observed in the present studies.

On the basis of these studies, it is proposed that a general attack occurs by the peroxydisulphate ion on the nitrogen of the amino group, which is present at the *p*-position in the sulpha drugs, to form a charged transition state (A) (step 1 where R represents different groups attached to the amino group, see Fig. 2) in the rate-determining step. The transition state formed in



step 1 then decomposes in a fast process, to give R–$\dot{N}$H and the sulphate radical ion ($SO_4^{\cdot-}$). The sulphate radical ion thus formed can attack another molecule of the sulpha drug to give another R–$\dot{N}$H. The R–$\dot{N}$H radicals couple with each other and can then be further oxidized by the peroxydisulphate ion to give the products.

REFERENCES

1 J.E. Leffler, J. Org. Chem., 20 (1955) 1202; 31 (1966) 533.
2 O. Exner, Nature (London), 201 (1964) 488; 227 (1970) 366; Collect. Czech. Chem. Commun., 29 (1964) 1094; 37 (1972) 1425; 38 (1973) 781; Chem. Scr., 3 (1973) 5.
3 D.A. House, Chem. Rev., 62 (1962) 185.
4 W.K. Wilmarth and A. Haim, Peroxide Reaction Mechanism, Wiley, New York, 1961, p. 175.
5 E.J. Behrman and J.O. Edwards, Rev. Inorg. Chem., 2 (1980) 179.
6 E.J. Behrman and J.E. McIsaac, Jr., Mech. React. Sulphur Comp., 2 (1968) 193.
7 A. Burger, Medicinal Chemistry, Interscience, New York, 2nd edn., 1960, p. 801.
8 R.L. Mayer and C. Oechslin, C.R. Acad. Sci., 205 (1937) 181.
9 Z.G. Szabo, L.J. Csanyi and H. Galiba, Z. Anal. Chem., 135 (1952) 269.
10 K.C. Khulbe and S.P. Srivastava, Agra Univ. J. Res. Sci. Part II, 85 (1965) 14.
11 S.P. Srivastava, A.K. Mittal and V.K. Gupta, Oxid. Commun., 2(2) (1981) 83.
12 S.P. Srivastava, A.K. Mittal and V.K. Gupta, React. Kinet. Catal. Lett., 17 (1981) 359.
13 V.K. Gupta, A.K. Mittal and S.P. Srivastava, Oxid. Commun., 2(2) (1981) 75.
14 I.M. Voladimir, A.O. Osip and A.Z. Yuria, Dipole Moments in Organic Chemistry, Plenum Press, New York, 1970.
15 H.N. Po and T.L. Allen, J. Am. Chem. Soc., 90 (1968) 1127.
16 A.R. Gallopo, J.O. Edwards and J.E. McIsaac, J. Am. Chem. Soc., 88 (1966) 3891.
17 L.R. Subbaraman and M. Santappa, Z. Phys. Chem., 4 (1966) 163; 48 (1966) 172.
18 E. Ben-Zui, J. Phys. Chem., 67 (1963) 2698; Inorg. Chem., 6 (1967) 1143.
19 D.E. Remy, R.E. Whitfield and H.L. Needless, Chem. Commun., (1967) 681.
20 P.R. Bontchev and A.A. Aleksiev, J. Inorg. Nucl. Chem., 32 (1970) 2237.
21 R.G. Pearson, J. Chem. Phys., 20 (1952) 1478.