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THERMODYNAMIC AND RELATED STUDIES FOR THE OXIDATION OF SULPHA DRUGS BY PERIODATE

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ABSTRACT

Various thermodynamic parameters, namely energy of activation E_a, enthalpy of activation $\Delta H^{\ddagger}$, free energy of activation $\Delta F^{\ddagger}$, entropy of activation $\Delta S^{\ddagger}$ and frequency factor A, for the oxidation of sulphanilamide, sulphacetamide, sulphadiazine, sulphaguanidine and sulphamethizole by periodate are reported and their role in the mechanism is discussed. All the reactions obeyed the Arrhenius equation, plots of log k against $1/T$ being linear. The validity of the isokinetic relationship and other related equations have been tested. An attempt has been made to correlate these findings with the nature of the transition state formed in the oxidation of sulpha drugs by periodate.

INTRODUCTION

Thermodynamic studies occupy an important place in deciding the nature of the mechanism of reactions in solution. The effect of temperature on the rate is studied 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 operative for the whole reaction series. The value of the isokinetic temperature β is used to decide whether the system is entropy controlled or enthalpy controlled. The differences in activation energies have been used, occasionally, as evidence of a change in the reaction mechanism. Sulpha drugs are the chief medical weapon against many bacterial diseases [3–6]. The oxidation of sulpha drugs is therefore of great importance. Periodate is a well-known oxidant and many of its reactions are of synthetic utility. However, a review of the literature on oxidations by periodate [7] indicated that no attempt has been made to study the effect of various thermodynamic parameters on the mechanism operative in the periodate oxidation of sulpha drugs.

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It was, therefore, considered worthwhile to initiate studies on some important oxidations by periodate and to decide the nature of the mechanism in these processes. Keeping this end in view, a systematic study of the various thermodynamic parameters has been made for the oxidation of sulphanilamide, sulphacetamide, sulphaguanidine, sulphadiazine and sulphamethizole by periodate in order to understand the nature of mechanism operative in the periodate oxidation of sulpha drugs. The validity of the Arrhenius equation, the isokinetic relationship and other related equations have been tested. The results of these studies are presented and discussed in this paper.

EXPERIMENTAL

The sodium metaperiodate used was of AnalaR grade (May and Baker). The sulpha drugs (all from IDPL, India) were used after several recrystallizations from hot water, or an appropriate organic solvent (sulphacetamide and sulphamethizole from methanol, and sulphadiazine from DMF–water), and dried in a vacuum. All other chemicals used were of analytical grade. The reactions were studied in aqueous medium.

The reaction between sulpha drugs and periodate resulted in the development of coloured solutions; the progress of the reactions was therefore followed spectrophotometrically on a Beckman DU-6 spectrophotometer by recording the absorbance at different times on a wavelength chosen for the drug under study. The different wavelengths chosen for the kinetics of different drugs, depending upon the λ_{max} of the product, are recorded in Table 1. The rates were then evaluated from the time versus absorbance plots by the plane mirror method [8]. The reactions were studied under pseudo-first-order conditions and the rates obtained under these conditions were then divided by the concentration of the reactant taken in excess to obtain the second-order rate constant, k. A similar method has been previously adopted for such types of reactions [9,10].

TABLE 1

Wavelengths chosen for the kinetics of reactions of different sulpha drugs with $NaIO_4$

Sulpha drug	Wavelength chosen for kinetic studies (nm)
Sulphanilamide	410
Sulphacetamide	360
Sulphaguanidine	341
Sulphadiazine	400
Sulphamethizole	375

All these reactions were found to follow an overall second-order kinetics, being first-order in periodate and first-order in sulpha drug. The second-order rate constants obtained as above were used to determine various thermodynamic parameters and for other studies.

RESULTS AND DISCUSSION

Thermodynamic parameters

The second-order rate constants were evaluated as described above for the oxidation of sulphanilamide, sulphacetamide, sulphaguanidine, sulphadiazine and sulphamethizole to evaluate the thermodynamic parameters: activation energy E_a, frequency factor A, entropy of activation $\Delta S^{\ddagger}$, enthalpy of activation $\Delta H^{\ddagger}$ and free energy of activation $\Delta F^{\ddagger}$. The second-order rate constants k evaluated at five different temperatures are recorded in Table 2. The Arrhenius equation relating temperature and rate constant, given by

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

was found to be obeyed, a plot between log k and $1/T$ being linear in each case, see Figs. 1–5. The activation energies were evaluated for these reactions from the slopes of the curves in Figs. 1–5. On the basis of these values of energy of activation, the values of different thermodynamic parameters were then determined by application of the following equations,

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

$$\Delta S^{\ddagger} = 19.147(\log k - 10.753 - \log T) + \frac{E_a}{T} \tag{3}$$

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

$$\Delta F^{\ddagger} = 19.147T(\log T + 10.319 - \log k) \tag{5}$$

TABLE 2

Reaction of different sulpha drugs with $NaIO_4$, second-order rates at different temperatures

Sulpha drug	$k \times 10^2$ (dm^3 mol^{-1} s^{-1})						
	298	303	308	313	318	323	328
Sulphanilamide	–	–	3.5	4.1	4.9	5.1	6.0
Sulphacetamide	–	4.8	5.5	8.0	9.3	12.0	–
Sulphadiazine	3.1	5.0	8.5	14.0	21.4	31.8	–
Sulphaguanidine	–	7.5	10.1	15.6	20.4	26.9	–
Sulphamethizole	–	–	3.1	3.8	5.3	6.9	9.9

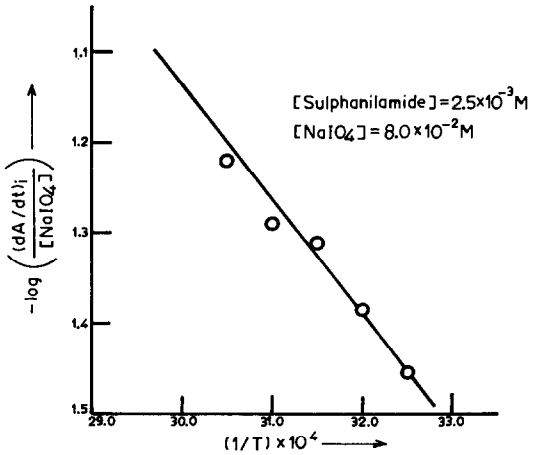


Fig. 1. Arrhenius plot: reaction of sulphanilamide with $NaIO_4$.

The mean values of various thermodynamic parameters thus calculated are given in Table 3. The data in Table 3 show that the reactions are characterized by large negative values for entropy of activation $\Delta S^{\ddagger}$. High negative values of $\Delta S^{\ddagger}$ are mainly observed in polar solvents and indicate that the solvation effects are predominant in these reactions and suggests the formation of a charged, rigid transition state which is expected to be strongly solvated. Because the reactions under study are ion–dipolar in nature [11], it is reasonable to expect that the entropy of the activated complex for all these reactions should be nearly the same. However, owing

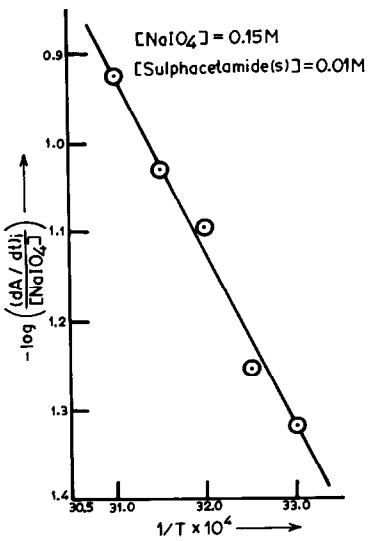


Fig. 2. Arrhenius plot: reaction of sulphacetamide(s) with $NaIO_4$.

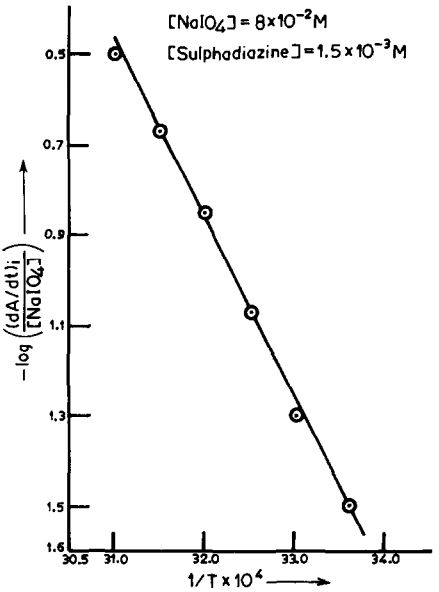


Fig. 3. Arrhenius plot: reaction of sulphadiazine with $NaIO_4$.

to the differences in polarity of the different drugs, the extent of solvation should be different and, hence, may cause variation in the observed $\Delta S^{\ddagger}$ values [12].

Low values of energy of activation E_a, as observed for the present reactions, are characteristic of bimolecular reactions in solution. Also, the

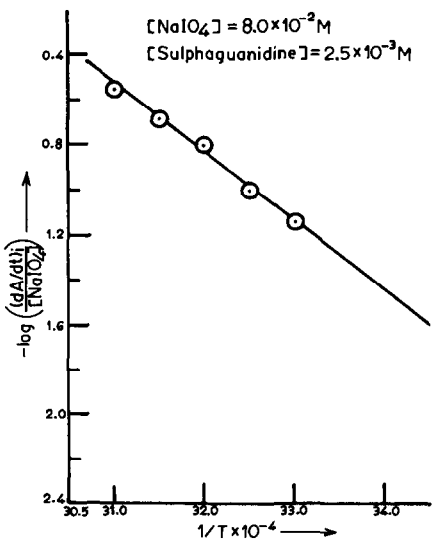


Fig. 4. Arrhenius plot: reaction of sulphaguanidine with $NaIO_4$.

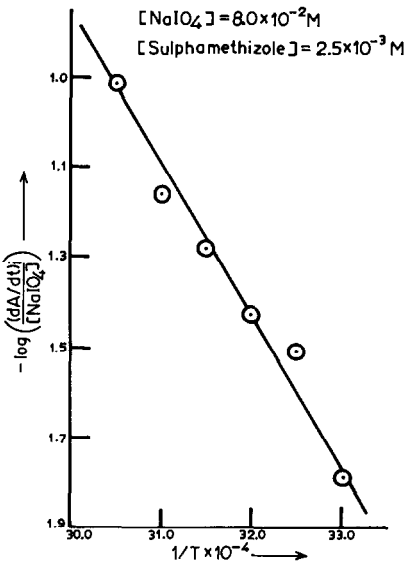


Fig. 5. Arrhenius plot: reaction of sulphamethizole with $NaIO_4$.

free energy of activation $\Delta F^{\ddagger}$ and the 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 processes should be similar. The value of the frequency factor A is of the order of 10^2, which suggests that the reacting species are rather large in size. Furthermore, the near constancy in the values of $\Delta F^{\ddagger}$ suggests that the site of attack is at the nitrogen of the amino group *para* to the amido group which is common in all the sulpha drugs. A slight variation in the rate for the different drugs may be accounted for by a change in the basic strength of the different drugs and, hence, by

TABLE 3

Reaction of different sulpha drugs with $NaIO_4$: kinetic parameters

Drug	E_a (kJ mol^{-1})	$-\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta F^{\ddagger}$ (kJ mol^{-1})	$A \times 10^2$
Sulphanilamide	21.1	212.9	18.5	86.2	9.8
Sulphamethizole	49.6	122.0	46.9	85.8	16.9
Sulphadiazine	75.4	29.5	72.8	81.9	55.9
Sulphaguanidine	53.5	98.8	50.8	81.9	48.2
Sulphacetamide	20.5	209.8	17.9	83.5	15.6

the availability of the loan pair on the nitrogen of the amino group *para* to the amido group for the reaction.

Validity of the isokinetic relationship and other related equations

The validity of the isokinetic relationship

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

(where β is the isokinetic temperature) was tested by plotting $\Delta S^{\ddagger}$ against $\Delta H^{\ddagger}$ (Fig. 6); the plot was found to be linear (correlation coefficient 0.990), thereby showing that the isokinetic relationship is obeyed for the oxidation of sulpha drugs. The validity of the isokinetic relationship suggests that the basic mechanism for all these reactions should be similar. The constancy in the $\Delta F^{\ddagger}$ values, as reported in Table 3, 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, $\Delta F^{\ddagger}$ values may be more or less constant with relative changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, as pointed out by Leffler [1]. The value of the isokinetic temperature, β, given by the slope of the plot in Fig. 6, was 290 K. Furthermore, Exner [2] has recommended an alternative method for checking 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 be calculated from the expression

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

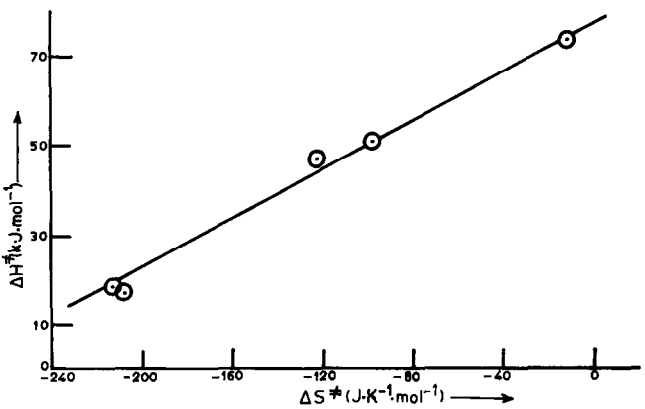


Fig. 6. Isokinetic plot.

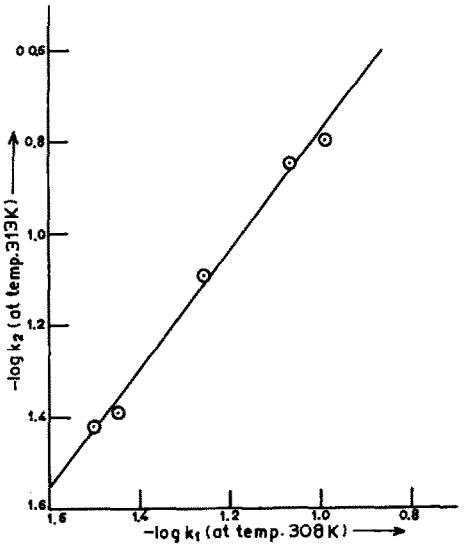
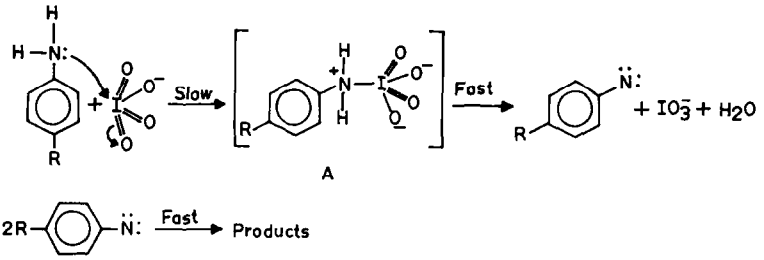


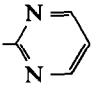
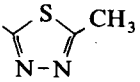
Fig. 7. Exner's plot: relationship between log k_2 (at 313 K) and log k_1 (at 308 K).

In the present studies, the plot of log k_2 (at 313 K) versus log k_1 (at 308 K) (Fig. 7) was 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 equations above was 295 K, which is in good agreement with that evaluated from the isokinetic plot. Thus the value of β is below the experimental temperatures employed in the present studies suggesting that these reactions are entropy controlled [13].

MECHANISM

Before proposing the nature of the mechanism for the oxidation of sulpha drugs, it is important to point out that the oxidation products were identified as the corresponding azobenzene derivatives and that radical scavengers had no effect on the rate, thus excluding the possibility of a radical mechanism. Therefore, on the basis of the above results an ionic mechanism is proposed in Scheme 1. This mechanism is in essence a polar one involving electrophilic attack on the loan pair of the nucleophilic amino group by the electron-deficient iodine of periodate in the rate-determining step forming a bimolecular S_N2-type charged transition state [A]. The transition state thus formed may rearrange in subsequent fast steps to give a nitrene molecule. Two nitrene molecules then couple to form the products. Similar transition



Scheme 1. R stands for $-SO_2NHCOCH_3$ for sulphacetamide, $-SO_2NH_2$ for sulphanilamide, $-SO_2NH-\overset{\overset{NH}{\|}}{C}-NH_2$ for sulphaguanidine, $-SO_2NH-$  for sulphadiazine and $-SO_2NH-$  for sulphamethizole.

states have previously been proposed for other reactions involving periodate [14].

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