Kinetics and Mechanism of Oxidation of 2,3-Dimethylindole by Potassium Peroxodisulphate

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The oxidation of 2,3-dimethylindole by potassium peroxodisulphate in dilute sulphuric acid media has been studied. The kinetic and spectrophotometric results indicate the formation of a detectable intermediate of unknown structure which decomposes to give 3-methylindole-2-carbaldehyde in low yield. The formation of the intermediate is first order in both 2,3-dimethylindole and peroxodisulphate whereas its decomposition is independent of oxidant concentration and acid-catalysed. The proposed mechanism is based on the assumption that the intermediate is a readily hydrolysable rearrangement product of the 2,3-dimethyl-3*H*-indol-3-yl sulphate formed from electrophilic attack of peroxodisulphate at C-3 involving nucleophilic displacement of peroxide oxygen.

In connection with our interest in the reactivity of β-carboline alkaloids, we have recently reported the oxidation of several *Rauwolfia* alkaloids by potassium peroxodisulphate.[1–3] Our results suggested that the reactions proceed *via* electrophilic attack of the oxidant at C-3 by a mechanism involving nucleophilic displacement of peroxide oxygen, rather than by a radical mechanism. Peroxodisulphate ions are known to react by various types of radical and non-radical mechanisms.[4–7] However, comparatively few reports of non-radical peroxodisulphate reactions have appeared. The best known examples are the oxidations of phenols (Elbs reaction)[8,9] and of aromatic amines (Boyland–Sims oxidation).[10–12]

We considered it of interest to extend our studies to simpler indoles, in order to find out whether their reactions follow the same mechanistic pattern. Despite the fact that oxidations of indoles by various familiar oxidants have been studied extensively,[13,14] the action of peroxodisulphate upon indoles has received little attention. It has been reported[15] that indole is oxidized by potassium peroxodisulphate in mildly acidic solutions to give indol-3-yl sulphate, which is hydrolysed to indol-3(2*H*)-one; the analogous oxidation of 3-methylindole[15,16] produces 3-methylindol-2(3*H*)-one together with a mixture of the isomeric 4-, 5-, 6-, and 7-hydroxy-3-methylindoles. However, the kinetics and mechanisms of these reactions have not been investigated.

Oxidations of three representative indoles (indole, 3-methylindole, and 2,3-dimethylindole) were studied initially. Peroxodisulphate oxidized indole to a complex mixture of polymeric products. The reaction with 3-methylindole was too fast to be followed by our experimental techniques. However, 2,3-dimethylindole (**1**), under controlled acidic conditions, reacted at measurable rates and gave simpler products. We report here a study of the kinetics of oxidation of this indole derivative.

Experimental

Reagents.—Indole, 3-methylindole, and 2,3-dimethylindole (**1**) (EGA-Chemie) were homogeneous on t.l.c. in several solvents systems and were used as received. Stock solutions of these compounds were prepared in methanol. Potassium peroxodisulphate and all other chemicals were of analytical grade (Merck).

Product Analysis.—A typical reaction mixture of the indole (**1**) and peroxodisulphate in sulphuric acid solution was monitored by u.v.–visible spectrometry in the region 240—400 nm. The spectral changes as a function of time are illustrated in Figure 1. At zero time the only absorption peak was at 282 nm, corresponding to the aqueous methanolic solution of (**1**). Initially, decreasing absorbance was observed at this wavelength with a displacement of the maximum to 286 nm and the appearance of a reddish-violet colour. Further, a new absorption band began to appear around 314 nm, at the expense of the 286 nm peak. Isosbestic points indicated that the transient was probably a direct precursor of the final 314 nm absorbing species. Under neutral or basic conditions the products were different and consisted principally of the degradation product *o*-aminoacetophenone.

The final product obtained under acidic conditions was isolated and characterized as follows. A solution of potassium peroxodisulphate (1.5 g) in 1:1 water–methanol was added dropwise to a stored acidic methanolic solution of 2,3-dimethylindole (0.85 g). The solution was then acidified with 30% v/v sulphuric acid, filtered to remove the precipitate of starting materials, and extracted with ether. The ether layer was washed with a dilute solution of sodium thiosulphate then water and finally dried (Na_2SO_4). Removal of solvent left an oil, which was chromatographed over alumina (30 g; activity II). Elution with 1:10 ether–benzene gave a small amount (0.068 g) of yellow material. After recrystallization from methanol, the product showed a u.v. spectrum in methanol similar to that of 3-methyl-2-carbaldehyde[17] ($\lambda_{max.}$ 312, 230, and 208 nm). The identity of this compound was confirmed from its ^1H and ^{13}C n.m.r. spectra [Varian XL-200 spectrometer; solvent $(CD_3)_2SO$]: $\delta(CHO)$ 10.0 (s); $\delta[C(2)]$ 132.6, $\delta[C(3)]$ 123.5, $\delta[C(4)]$ 127.7, $\delta[C(5)]$ 121.4, $\delta[C(6)]$ 119.9, $\delta[C(7)]$ 127.0, $\delta[C(8)]$ 112.9, $\delta[C(9)]$ 138.0, $\delta(CH_3)$ 8.4, and $\delta(CHO)$ 181.9.

Our attempts to isolate the intermediate absorbing at 286 nm were unsuccessful; it suffers rearrangement or degradation during preparative work-up in acidic or basic media, respectively.

Kinetic Measurements.—Kinetic experiments were performed under pseudo-first-order conditions with a large excess of peroxodisulphate. The reaction rates were determined by monitoring the disappearance of the indole (**1**) at 282 nm or the appearance of the final product at 312 nm (Perkin-Elmer Lamba-5 spectrophotometer equipped with temperature-controlled cell-holder). The temperature was maintained to within ±0.1 °C.

Simple kinetics were not observed. The changes in absorbance showed a relatively rapid variation and then a slower regular variation with time, indicating two different

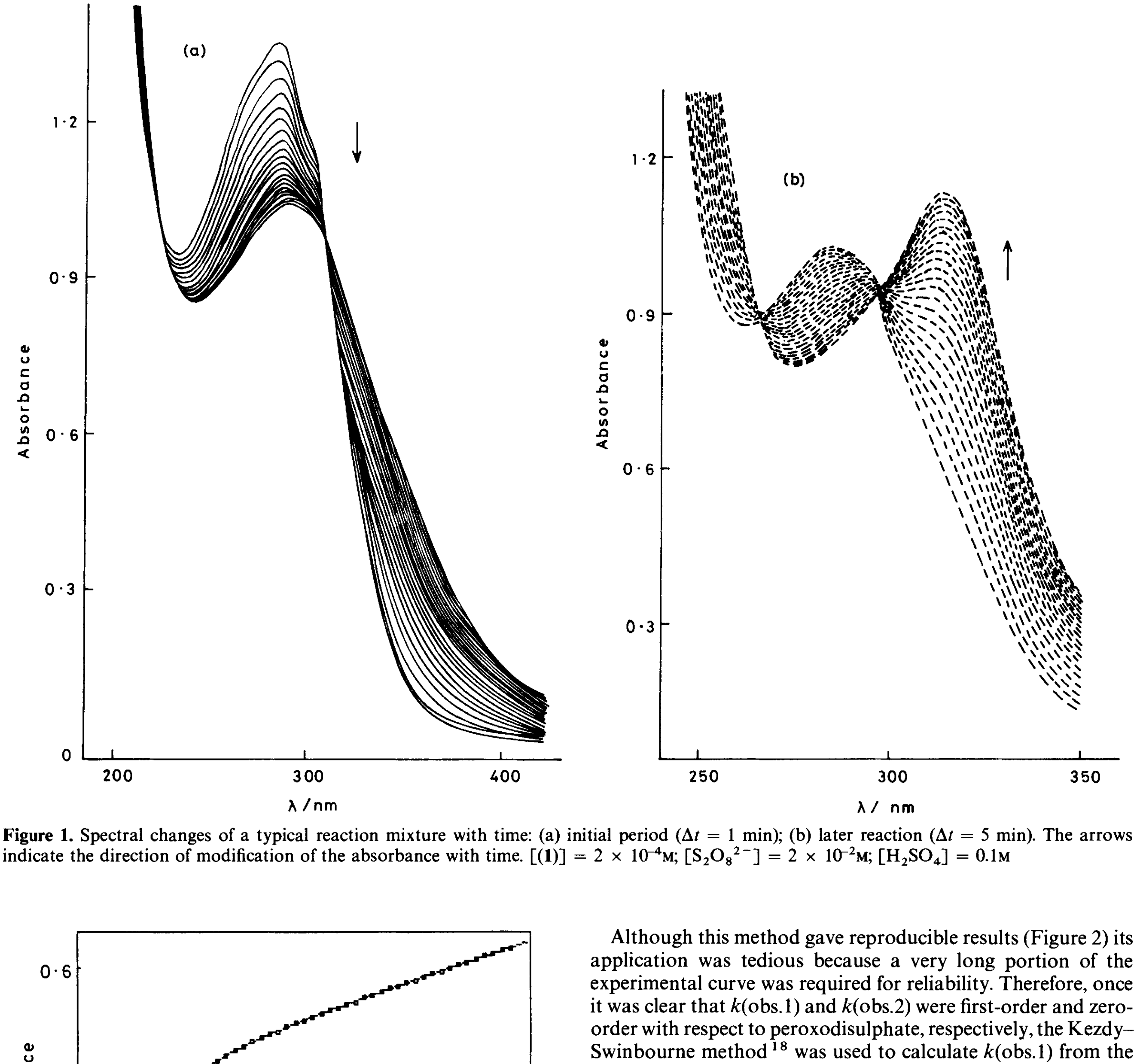


Figure 1. Spectral changes of a typical reaction mixture with time: (a) initial period (Δt = 1 min); (b) later reaction (Δt = 5 min). The arrows indicate the direction of modification of the absorbance with time. [(**1**)] = 2 × 10^{-4}M; [$S_2O_8^{2-}$] = 2 × 10^{-2}M; [H_2SO_4] = 0.1M

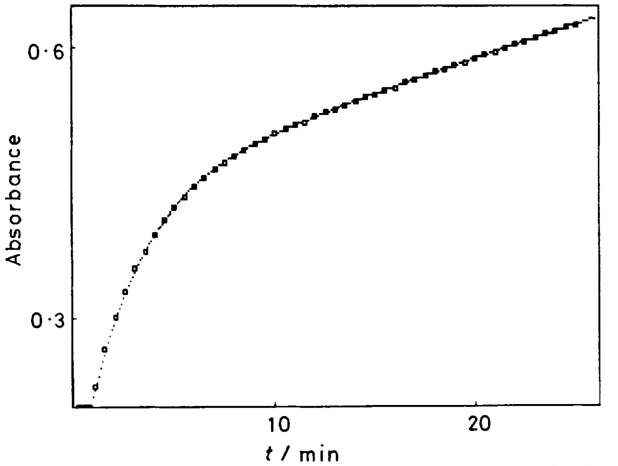


Figure 2. Plot of absorbance at 312 nm against time; [(**1**)] = 2 × 10^{-4}M; [$S_2O_8^{2-}$] = 5 × 10^{-2}M; [H_2SO_4] = 0.1M

reactions. In preliminary experiments the rate constants were obtained by non-linear least-squares fitting of absorbance *versus* time to equation (1), in which D_t is the absorbance of the mixture.

$$D_t = A + Be^{-k(\mathrm{obs.1})t} + Ce^{-k(\mathrm{obs.2})t} \qquad (1)$$

Although this method gave reproducible results (Figure 2) its application was tedious because a very long portion of the experimental curve was required for reliability. Therefore, once it was clear that k(obs.1) and k(obs.2) were first-order and zero-order with respect to peroxodisulphate, respectively, the Kezdy–Swinbourne method[18] was used to calculate k(obs.1) from the first part of the absorbance–time curve.

This method is based on equation (2), where τ is a time

$$D_t = D_\infty\{\exp[k(\mathrm{obs.})\tau] - 1\} + D_{t+\tau}\exp[k(\mathrm{obs.})\tau] \qquad (2)$$

interval. In order to obtain accurate values of k(obs.) different τ values for each kinetic run were used, to obtain experimental k(obs.)τ values from the plots of D_t against $D_{t+\tau}$. Then, the rate constant was calculated from the slope of the plot of these k(obs.)τ values against τ. An example of such calculations is showed in Figure 3. Results of replicate runs were found to be reproducible to within ±5—8% (within experimental error).

Results

The values of k(obs.1) at various initial concentrations of 2,3-dimethylindole (**1**) and $S_2O_8^{2-}$ are reported in Table 1. This reveals that an increase in concentration of peroxodisulphate causes a proportional increase in the rate constants. A plot of k(obs.1) *versus* [$S_2O_8^{2-}$] is a straight line passing through the origin. On the other hand, the constancy of k(obs.1) at fixed peroxodisulphate concentration over a range of indole

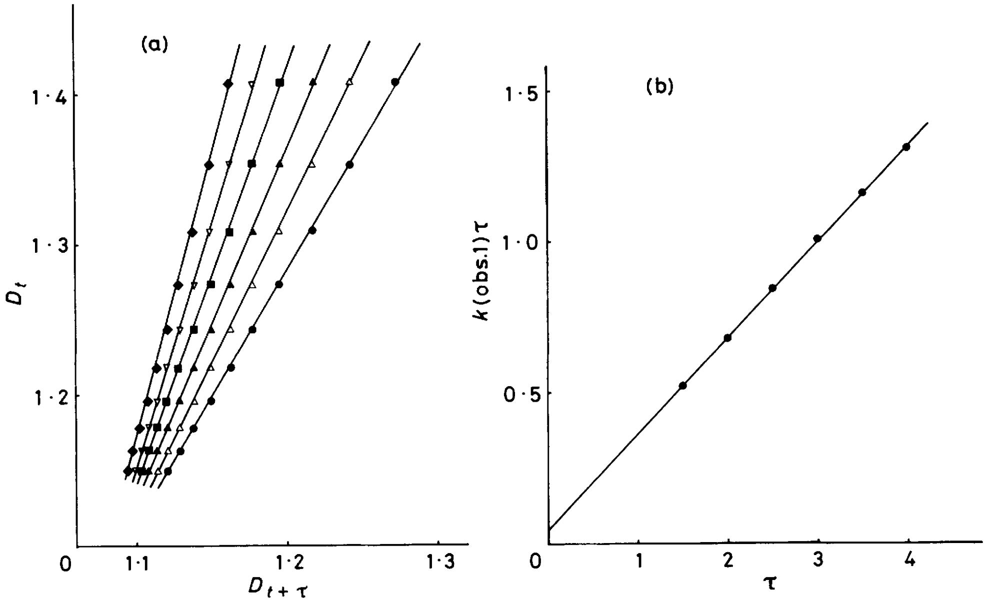


Figure 3. Plots of (a) D_t against $D_{t+\tau}$ and (b) $k_{(\text{obs.1})}\tau$ against τ; λ = 282 nm; [(**1**)] = 2×10^{-4}M; [$S_2O_8^{2-}$] = 5×10^{-2}M; [H_2SO_4] = 0.1M

Table 1. Pseudo-first-order rate constants, *k*(obs.1) and *k*(obs.2), for the oxidation of 2,3-dimethylindole (**1**) by peroxodisulphate at 25 °C in 0.1M-sulphuric acid and 20% v/v methanol–water

10^4[(**1**)]/M	10^2[$S_2O_8^{2-}$]/M	*k*(obs.1)/min^{-1}	*k*(obs.2)/min^{-1}
2	1	0.062	
1	2	0.117	
2	2	0.114	
4	2	0.112	
2	3	0.203	3.9×10^{-3}
2	4	0.267	2.6×10^{-3}
2	5	0.314	3.4×10^{-3}
2	6	0.387	
2	7	0.452	
2	9	0.570	3.6×10^{-3}

Table 2. Dependence of the rate constant (*k*) on temperature; [H_2SO_4] = 0.1M; 20% v/v methanol–water

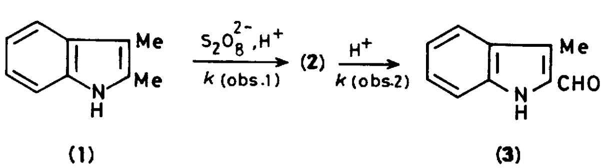
T/°C	20	25	30	35	40
k/l mol^{-1} s^{-1}	0.072	0.094	0.134	0.182	0.257

concentrations is in agreement with first-order dependence on the concentration of the latter. Hence, the rate law (3) can be

$$v = k(\text{obs.1})\,[(\mathbf{1})] = k[S_2O_8^{2-}]\,[(\mathbf{1})] \qquad (3)$$

proposed for the formation of the intermediate, where *k* is the overall second-order rate constant. Values of *k* at different temperatures are summarized in Table 2. From the temperature dependence of *k*, the activation parameters $\Delta H^\ddagger$ = 46.4 kJ mol^{-1} and $\Delta S^\ddagger$ = -107 J mol^{-1} K^{-1} were calculated. As can be seen in Table 1 the rate constant *k*(obs.2) was independent of peroxodisulphate concentration.

The reactions were also studied at various hydrogen ion concentrations, obtained by the addition of sulphuric acid. The appearance of 3-methylindole-2-carbaldehyde was accelerated by an increase in sulphuric acid concentration. However, the rate of formation of the intermediate, *k*(obs.2), was independent of acidity up to 1M-sulphuric acid, although it is clear that an acidic medium is necessary for this reaction. In neutral or basic media, the intermediate is not formed and the overall reaction yields different degradation products. The values of *k*(obs.2) in 0.1M- and 0.5M-sulphuric acid were 3.4×10^{-3} and 5.6×10^{-3} min^{-1}, respectively. Unfortunately, it was not possible to conduct a more thorough study of acidity influence on *k*(obs.2) over a wider range, since at higher acidities the two stages of the reaction are more closely coupled and data analysis becomes more difficult.

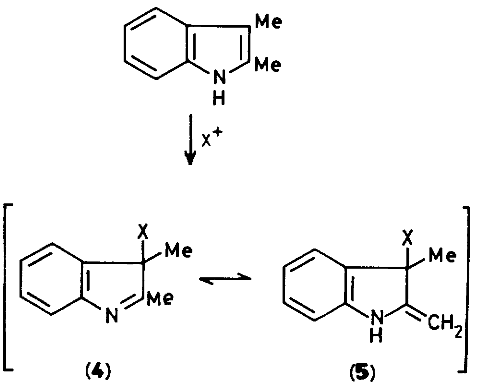


Scheme 1.

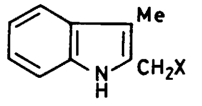
In order to elucidate the mechanism of the reactions, experiments were carried out to find out whether free radicals are formed. The results of kinetic runs in the presence of Ag^+ (10^{-5}—10^{-6}M), well known as a radical promotor in peroxodisulphate reactions, and allyl alcohol (0.05—0.1M), an effective sulphate-radical trap, showed no detectable effect on *k*(obs.1); therefore these results are not reported.

Discussion

The kinetic and spectral results indicate that, under controlled acidic conditions, 2,3-dimethylindole (**1**) reacts with peroxodisulphate ions to give, through the formation of a detectable intermediate (**2**), 3-methylindole-2-carbaldehyde (**3**). The same reaction pattern has been observed in the oxidation reactions of 2,3-dimethylindole and other 2-alkylated indoles with several oxidants such as oxygen and peroxides,[19—21] periodic acid,[22] and selenium dioxide.[23] Although different mechanisms have been proposed for these reactions,[20—22,24] they usually begin with the formation of a 3*H*-indole (**4**) intermediate formed by electrophilic attack of the oxidant or some species derived from it (X^+) on C-3. This step is followed by an acid-catalysed



Scheme 2.



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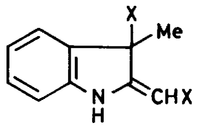

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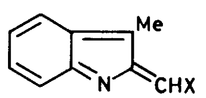


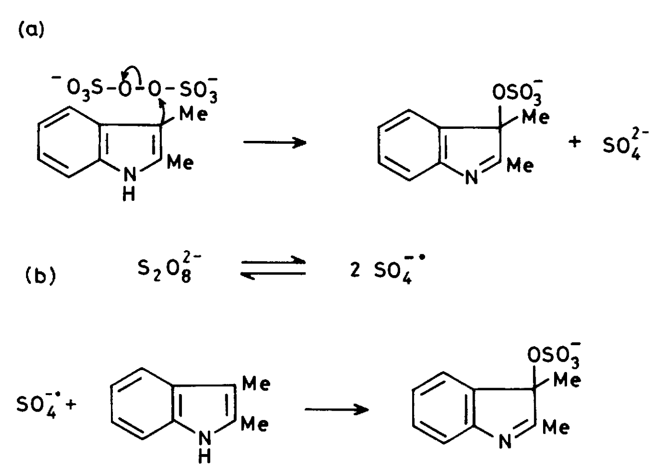
(8)

tautomeric equilibration of the 3*H*-indole and its enamine form (5).

Since peroxodisulphate ions are known to be mildly electrophilic reagents capable of substituting activated aromatic compounds, it seems reasonable to assume that this mechanism applies to the present oxidation. Thus, it appears that 2,3-dimethyl-3*H*-indol-3-yl sulphate ($X = OSO_3^-$) may be involved in this reaction. Similar intermediates have been detected in or suggested for the oxidations of indoles and other organic substrates by peroxodisulphate.[1,2,9,10,15]

However, although the 3-sulphate may be the primary product in this reaction, it is unlikely to be the intermediate absorbing at 286 nm: 3*H*-indoles are known to be highly unstable under the experimental conditions used in our studies, and they absorb light at shorter wavelength than the parent indoles.[25–27] Therefore, it seems more reasonable that this intermediate comes from some reaction or rearrangement of the 3*H*-indole.

The spectroscopic properties of this intermediate resemble those reported[25] for the rearrangement product of 3-chloro-2,3-dimethyl-3*H*-indole resulting from the chlorination of 2,3-dimethylindole by t-butyl hypochlorite. Although the structure of this species was not established, the structures (5) and (6) were considered the most probable. The latter (6) has since been isolated and characterized.[27,28] Others[26] have also detected similar types of compound as the principal products in the trifluoroacetylation of 2,3-dimethylindole, together with smaller amounts (6%) of a third product for which the structure (7) was suggested. It seems reasonable therefore to assume one or another of these structures for the intermediate in the present reaction.



Scheme 3.

Although the reaction of a second $S_2O_8^{2-}$ molecule at the enamine group or the rearrangement of the electrophile from C-3 to the side-chain position (2-CH_2) is possible, we cannot provide kinetic evidence for such reactions. All the kinetic results concerning intermediate formation point to initial electrophilic attack to form the 3*H*-indole as the rate-determining step (Scheme 3). The observed second-order rate law and the magnitude of the activation parameters, particularly the highly negative $\Delta S^\ddagger$ value, are as expected, according to Edwards,[5,6] for a nucleophilic displacement on the peroxide linkage [Scheme 3, mechanism (a)]. Homolytic cleavage of the peroxodisulphate ions prior to electrophilic attack [Scheme 3, mechanism (b)] is not consistent with the absence of catalytic effects in the presence of either inhibitors or initiators of radicals.

On the other hand, the absence of an acid catalysis effect on k(obs.1) indicates that it is the unprotonated 2,3-dimethylindole which is reactive for the sulphuric acid concentration range (0.1—1M) used in our work. 2,3-Dimethylindole is a weak base (pK -1.49).[29] The necessity of an acid medium for the reaction is probably related to the stabilization of the enamine form of 2,3-dimethyl-3*H*-indol-3-yl sulphate or its rearrangement to generate the intermediate.

From the common kinetic features in this and other oxidation reactions of indoles by peroxodisulphate, it is clear that the general pattern in these reactions is the initial electrophilic attack of peroxodisulphate on C-3 of the indole ring, with displacement of sulphate ion to generate a 3*H*-indol-3-yl sulphate intermediate. The nature of the final products differs according to the structural characteristics of the 3*H*-indole and the reaction medium. Thus, in the case of the *Rauwolfia* alkaloids previously studied,[1–3] the presence of an electron pair on the non-indolic nitrogen atom of the tetrahydro-β-carboline skeleton favours an aromatization process.

In the reaction under study, the mechanistic details of the step in which 3-methylindole-2-carbaldehyde is formed are less clear, since the structure of the intermediate from the 3*H*-indole rearrangement is unknown. However, the lack of dependence of k(obs.2) on peroxodisulphate concentration and the observed acid catalysis suggest a hydrolytic mechanism, probably involving protonation as a rate-determining step. It is tempting to consider a sulphate ester structure such as (7) or (8) for the intermediate. Either of these compounds would be readily hydrolysable to an aldehyde.[30,31]

This suggestion is supported by the low yield of the oxidation of 2,3-dimethylindole to the aldehyde [compound (7) is only a minor product in the electrophilic substitution of 2,3-dimethylindole][26,32] and by the reddish-violet colour of the solutions of the intermediate, which is characteristic of azafulvenium compounds such as (**8**).

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