Direct Evidence on the Mechanism of the Oxidation of 2,3-Dimethylindole by Inorganic Peroxo Anions

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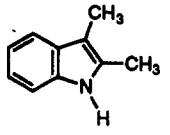
The mechanisms of the 2,3-dimethylindole (1) oxidation to 3-methylindole-2-carbaldehyde (3) by peroxodisulfate and peroxomonosulfate anions have been investigated in H_2SO_4/20% v/v methanol–water solutions. Because indolenines have been postulated as intermediates in the oxidation of some indole derivatives, we have also analyzed the reactivity of 3-hydroxy-2,3-dimethyl-3*H*-indole (**2a**) with both peroxo anions. From these and previous studies, it is concluded that the reactions proceed in three steps: electrophilic attack of the peroxidic bond at the C-3 atom of indole to form the indolenine intermediate, a second peroxo anion attack on the enamine tautomer of this intermediate followed by hydrolysis to give 3-methylindole-2-carbaldehyde (3).

Introduction

We have recently reported that the oxidation of 2,3-dimethylindole (1) by peroxodisulfate anions (PDS) to give 3-methylindole-2-carbaldehyde (3) proceeds in two kinetically distinguishable phases: formation of a detectable intermediate and its subsequent slower acid-dependent hydrolysis.[1] The proposed mechanism was based on the assumption that the intermediate is a readily hydrolyzable rearrangement product of the 2,3-dimethyl-3*H*-indol-3-yl sulfate (**2b**) initially formed from electrophilic attack of PDS at the C-3 atom. However, since the reactivity of this intermediate was too low for precise kinetic measurements on the second step, the mechanism of this step remained rather obscure.



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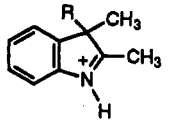

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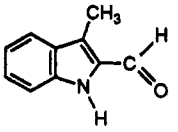
a: R = OH
b: R = OSO_3H
c: R = OOH



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In fact, although it is widely accepted that for the electrophilic substitutions in indole 1 the reaction pathway starts with the conversion of the indole to the 3-R indolenine derivatives,[2-4] there is, however, a considerable range of opinion about the details of the latter steps.[5-8] Depending on the nature of the R-group and the substituents in the indole ring, different mechanisms for the subsequent steps can be postulated. A product such as aldehyde 3 could be satisfactorily accounted for by the formation of an enamine tautomer followed by intramolecular rearrangement of the R group and subsequent hydrolysis.[7] Also, as it has been pointed out,[6] the substituent at C-3 in the enamine tautomer could be displaced by an external attack (a new peroxo anion molecule) at the exocyclic double bond of the enamine.

In this paper, we have tried to obtain further information in order to build up a more detailed mechanistic picture for this oxidation reaction. With this purpose we have selected peroxomonosulfate (PMS) as the oxidizing agent. This peroxo anion was chosen because of the following two main reasons. Firstly, its distinctive reactivity[9,10] is appropriate for an independent and precise kinetic study on the steps of the mechanism. Secondly, the proposed indoleninic intermediate for this reaction, compound **2a**, can be synthesized and isolated by the method described in the literature.[11,12] Therefore, this will allow us a straightforward comparison between the kinetic behavior of the intermediate directly formed in the reaction media or obtained by an independent procedure.

Thus, in the present work, we have carried out a kinetic study of the influence of PMS concentration and acidity on the two steps of indole 1–PMS reaction. Moreover, we have synthesized indolenine **2a** and analyzed its reactivity against PMS under the same experimental conditions. Also, we have isolated the indoleninic intermediate from 1–PMS reaction media and confirmed it to be compound **2a**.

Finally, we have also tried to isolate the intermediate of the 1–PDS reaction, indolenine **2b**. Unfortunately, although we have some pieces of evidences on the nature of this compound, we were unable to isolate and identify it without ambiguity. For this reason, we have supposed the indolenine **2a** to be an adequate model compound for this intermediate, and a kinetic study of the influence of PDS concentration and acidity on the **2a**–PDS reaction has also been carried out.

Experimental Section

Reagents. 2,3-Dimethylindole (1) (Aldrich Quimica) was used as received. Stock solutions of this compound were prepared in methanol. Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) was also purchased

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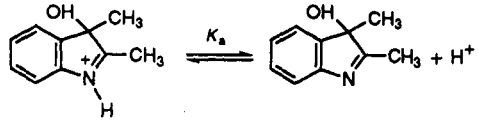
Scheme I



from Aldrich Quimica. Potassium peroxodisulfate and other chemicals were Anala R grade (Merck).

Synthesis. Compound **2c** was prepared by a literature method.[12] Indolenine **2a** was obtained according to the directions of Beer[11] but reducing approximately by 10-fold the reactant concentrations and dissolving **2c** in a (5:1 v/v) petroleum ether (bp 40–60 °C)–ethyl acetate mixture. These modifications avoid the dimer formation.[13]

On the other hand, compound **2a** was isolated from the reaction media by the following procedure. The indole 1 (100 mg) was dissolved in the minimum amount of methanol–water (50:50 v/v) and vigorously stirred in an ice bath. Ethyl acetate was added to prevent crystallization on cooling. Once the solution was clear, PMS (180 mg) in H_2SO_4 0.1 M (20 mL) was added and the solution was immediately made basic, pH = 9–10 with 5% KOH solution. After two extractions with petroleum ether (bp 40–60 °C) to eliminate the remaining 1, the indolenine was extracted from the aqueous layer with three portions of dried diethyl ether (25 mL each). Evaporation of the ether layer yielded a cream solid (10 mg) whose UV–visible, NMR, and mass spectra were identical to those of indolenine **2a** previously prepared.[11]

Determination of Ionization Constants. Ionization data of indolenine **2a** were obtained spectrophotometrically by the usual procedure, i.e. from absorbance measurements at selected wavelenghts of the free acid, the conjugate base, and some of their mixtures, Scheme I. The ionization constant was calculated by using the standard Henderson–Hasselbach equation. Stock solutions of **2a** were made in methanol, and the buffer solutions for UV–vis spectrophotometry (potassium chloride/hydrochloric acid or citric acid/sodium hydroxide) were prepared at constant ionic strength (I = 0.1). The pK_a value was 2.47 ± 0.08.

Kinetic Measurements. Kinetic experiments were performed under pseudo-first-order conditions with a large excess of PMS or PDS anions. The first step of the reaction between 1 and PMS was studied by monitoring the disappearance of the indole 1 at 282 nm. The rate of the second step and the reaction rates betwen **2a** and PMS or PDS were determined by the absorbance increase at 252 nm. In all cases, the plots of absorbance vs time indicate the lack of overlap between the first and second step of the reaction. Moreover, for the second step we have also carried out some measurements at 312 nm just to check that the rate constants were the same as those obtained at 252 nm. When necessary, a rapid kinetic accessory was used. All the reactions were followed in a computer-interfaced spectrophotometer. The evolution of the spectra of the mixtures with time was recorded with a Hewlett-Packard 8452A diode array spectrophotometer. The temperature was always maintained to within ±0.1 °C. Pseudo-first-order rate constants were obtained by a nonlinear least-square fitting of the absorbance–time data to eq 1,

$$A_t = A_\infty + (A_0 - A_\infty)\exp(-k_{obs}t) \quad (1)$$

Usually, an excellent agreement between experimental and calculated A_t values was obtained. Rate constants in duplicate runs were reproducible to within better than 5%.

Results

For the indole 1–PMS reaction, the spectral changes in 0.1 M H_2SO_4 as a function of time are illustrated in Figures 1 and 2. As these Figures show, two clearly distinguishable steps can be observed. Thus, initially there is a speedy decrease of the absorbance at 282 nm corresponding to the transformation of indole 1 into its indoleninic intermediate **2a**. This decrease of absorbance is accompanied

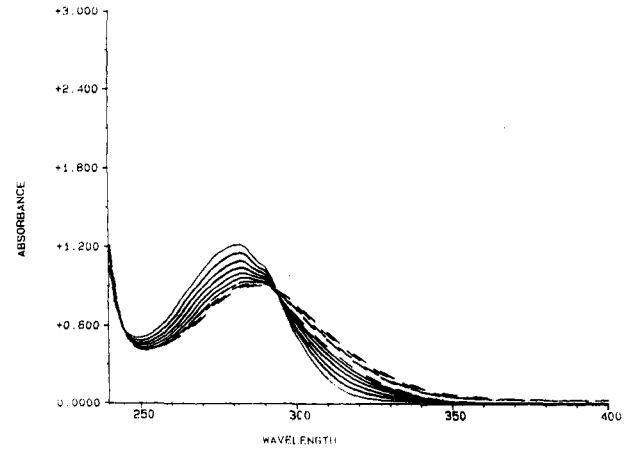


Figure 1. Changes in UV spectra (at 2-second intervals) for a typical reaction mixture. [1] = 2 × 10^{-4} M, [PMS] = 2 × 10^{-3} M, [H_2SO_4] = 0.5 M.

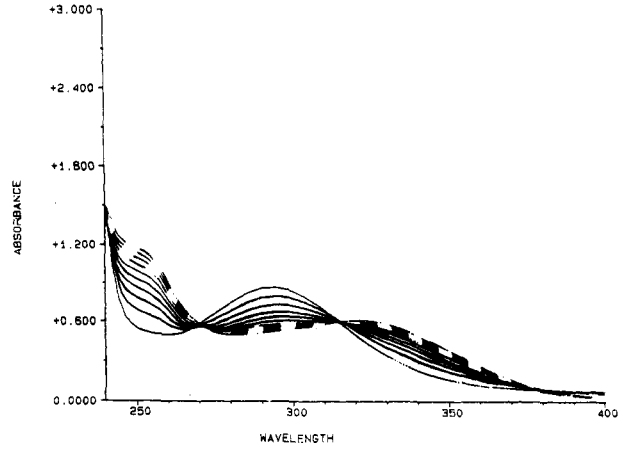


Figure 2. Changes in UV spectra (at 1-min interval, and 1 min of delay time) for a typical reaction mixture. [1] = 2 × 10^{-4} M, [PMS] = 2 × 10^{-3} M, [H_2SO_4] = 0.5 M.

by a slight displacement of the maximun toward 290 nm which is characteristic of the protonated indolenine intermediate. The clean isosbestic points indicate the direct transformation of indole 1 into indolenine **2a**. Furthermore, once the indolenine has been accumulated, a new absorption band begins to appear slowly around to 312 nm at the expense of the 290 nm peak and again with clear isosbestic points. Also, there is an absorbance increase at 252 nm, the wavelength selected to study this second step (Figure 2). As Figure 2 shows, this second step corresponds to the later conversion of the indolenine intermediate **2a** into the aldehyde **3**.[1,14] The identification of this product was made as in the previous paper.[1]

All the kinetic runs have been carried out in sulfuric acid concentration ≥0.1 M, because the indolenine reactivity depends on its protonation state. In fact, when the reactions are studied at lower acid concentrations, the spectral changes with time of the reaction mixtures are different from those shown in Figures 1 and 2. Moreover, the final spectrum is not that of aldehyde 3. Because we were only interested in the mechanism of oxidation of indole 1 to aldehyde 3, kinetic experiments have not been carried out at these higher pH values.

At this point, it should be realized that indolenines are themselves unstable under different experimental con-

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Table I. Pseudo-First-Order Rate Constants k(obs.1) and k(obs.2) for the Oxidation of 2,3-Dimethylindole (1) by Peroxomonosulfate in 20% v/v Methanol–Water. [1] = 2 × 10^{-4} M and [H_2SO_4] = 0.1 M

10^3[PMS]/M	T/K	10^2k(obs.1)/s^{-1}	10^3k(obs.2)/s^{-1}
1.0	298	2.79	2.87
1.5	298	4.05	4.02
2.0	298	5.45	5.80
2.5	298	6.79	6.93
3.0	298	7.83	8.40
2.0	293	4.36	4.57
2.0	303	6.52	7.57
2.0	308	7.83	9.44
		$\Delta H^{\ddagger}$ = 26 ± 3 kJ/mol	$\Delta H^{\ddagger}$ = 34 ± 0.5 kJ/mol
		$\Delta S^{\ddagger}$ = −180 ± 8 J/K mol	$\Delta S^{\ddagger}$ = −172 ± 2 J/K mol

ditions. Thus, rearrangement and dimerization reactions have been observed to occur even in neutral media.[7] Therefore, we wanted to ascertain whether **2a** could give, in acid media, compound **3**. The spectral analysis has shown that although **2a** is in fact unstable in 0.1 M H_2SO_4, it decomposes very slowly to afford a final product different to compound **3**.

In order to elucidate the mechanism of the reactions, other studies have been performed to find out whether free radicals are involved. The results of kinetic runs in the presence of Ag^+, well known as a radical promotor, showed no detectable effect on either the rate of disappearance of **1** or the rate of appearance of the product **3**; therefore these results are not reported. The influence of allyl alcohol could not be studied because the indolenine solution themselves were unstable in the presence of this radical trap.

Also, because ions differently charged can be involved in the second step of the reactions, we decided to analyze the influence of the ionic strength, I, on these processes. With this purpose, we studied the effect of varying $NaClO_4$ and $NaHSO_4$ concentration (range 0–0.6 M) on reactivity. Whereas the increase of the ionic strength does not affect the first step of the reactions, it produces a marked decrease on the rate constants of the second phases. Moreover, plots of log k_{obs} *vs* $I^{1/2}$ are surprisingly linear. As an example, for the **2a**–PMS reaction these plots give slopes and intercepts of −0.4 ± 0.1, −0.6 ± 0.1, and −2.10 ± 0.06, −2.05 ± 0.09 for $NaHSO_4$ and $NaClO_4$, respectively.

In all cases, the measured rate constants at fixed PMS or PDS and acid concentration were the same over a range of indole or indolenine concentration. This is in agreement with first-order dependence on the concentration of the later reactants.

The values of the rate constants for the first step k(obs.1) and second step k(obs.2) of the **1**–PMS reaction are reported in Table I. In Table I, the influence of PMS concentration and temperature is included together with the activation parameters for both steps. The same kind of data are collected in Table II for the **2a**–PMS reaction. As data in Tables I and II show, an increase in concentration of PMS causes a proportional increase in the rate constants for the conversion of **1** into **2a** and **2a** into **3**. At this point, it should be emphasized that there is completely similar kinetic behavior of the **2a**–PMS reaction independently of whether the indolenine is formed in the reaction media or just synthesized by a different way. This fact is in agreement with **2a** being the intermediate in the **1**–PMS reaction. The plots of k(obs.1), k(obs.2), and k'(obs.2) against PMS concentration are straight lines passing through the origin with slopes 26 ± 2 M^{-1} s^{-1} (r = 0.999), 2.8 ± 0.3 M^{-1} s^{-1} (r = 0.998), and 3.2 ± 0.3 M^{-1} s^{-1} (r = 0.999), respectively.

Table II. Pseudo-First-Order Rate Constants for the Oxidation of 3-Hydroxy-2,3-dimethyl-3*H*-indole (2a) by Peroxomonosulfate in 20% v/v Methanol–Water. [2a] = 2 × 10^{-4} M and [H_2SO_4] = 0.1 M

10^3[PMS]/M	T/K	$10^3k'$[obs.2]/s^{-1}
1.0	298	3.41
1.5	298	5.29
2.0	298	6.55
2.5	298	8.36
3.0	298	9.98
2.0	293	5.30
2.0	303	8.43
2.0	308	10.54
		$\Delta H^{\ddagger}$ = 32 ± 3 kJ/mol
		$\Delta S^{\ddagger}$ = −180 ● 8 J/K mol

Table III. Pseudo-First-Order Rate Constant for the Oxidation of 3-Hydroxy-2,3-dimethyl-3*H*-indole (2a) by Peroxodisulfate in 20% Methanol–Water. [2a] = 2 × 10^{-4} M and I = 0.6

[PDS]/M	[H_2SO_4]/M	T/K	$10^4k''$(obs.2)/s^{-1}
0.0125	0.25	298	0.78
0.025	0.25	298	1.23
0.050	0.25	298	1.83
0.075	0.25	298	1.92
0.100	0.25	298	2.11
0.050	0.10	298	0.88
0.050	0.20	298	1.42
0.050	0.40	298	2.29
0.050	0.50	298	2.48
0.025	0.25	303	1.69
0.025	0.25	308	2.26
		$\Delta H^{\ddagger}$ = 43 ± 4 kJ/mol	
		$\Delta S^{\ddagger}$ = −175 ± 15 J/K mol	

The reactions with PMS have also been studied at various hydrogen ion concentrations, obtained by the addition of sulfuric acid. The range of acidity was chosen to ensure the protonation of the indolenine intermediate (pK_a = 2.47 ± 0.08). While the disappearance of 2,3-dimethylindole was independent on sulfuric acid concentration, the rate of appearance of 3-methylindole-2-carbaldehyde decreased in both cases with the increase of sulfuric acid concentration. This effect is completely similar to that observed on changing $NaHSO_4$ or $NaClO_4$ concentrations. In fact, for the reaction between **2a** and PMS at varying sulfuric acid concentration, log k_{obs} *vs* $I^{1/2}$ is also linear with slope and intercept equal to −0.56 ± 0.04 and −2.07 ± 0.04, respectively. Moreover, the rate constants do not change on changing sulfuric acid concentration while the ionic strength is kept constant by the addition of $NaHSO_4$ salt. All these facts indicate the nonexistence of a specific effect of acidity on the mechanism of this second step of the reaction and confirm the protonated indolenine and the monoanionic species of PMS to be the reactants under our experimental conditions.

Table III contains data of the influence of PDS concentration and acidity on the rate constants for the reaction between **2a** and PDS at constant ionic strength kept by the addition of $NaHSO_4$ salt. As can be seen inTable III, an increase in PDS concentration produces an increase in the rate constant values. However, in this case the plot of k''(obs.2) versus the oxidant concentration is indeed curved. In fact, it is the reciprocal of k''(obs.2) which changes linearly with the reciprocal of PDS concentration. The slope and intercept of such a plot are (1.2 ± 0.1)10^2 M s and (3.5 ± 0.4)10^3 s, respectively. Finally,

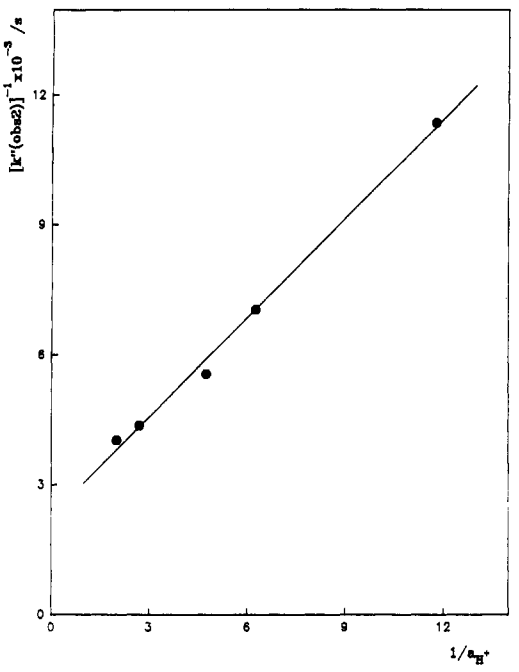


Figure 3. Dependence of reciprocal of the rate constant on reciprocal of proton activity for the **2a**–PDS reaction.

with respect to the influence of acid concentration in this reaction, an increase in the rate constant is observed on increasing sulfuric acid concentration. Thus, as Figure 3 shows, the plot of $[k''(obs.2)]^{-1}$ against the reciprocal of proton activity[15] is linear with slope of $(7.6 \pm 0.8)10^2$ s and intercept of $(2.3 \pm 0.5)10^3$ s.

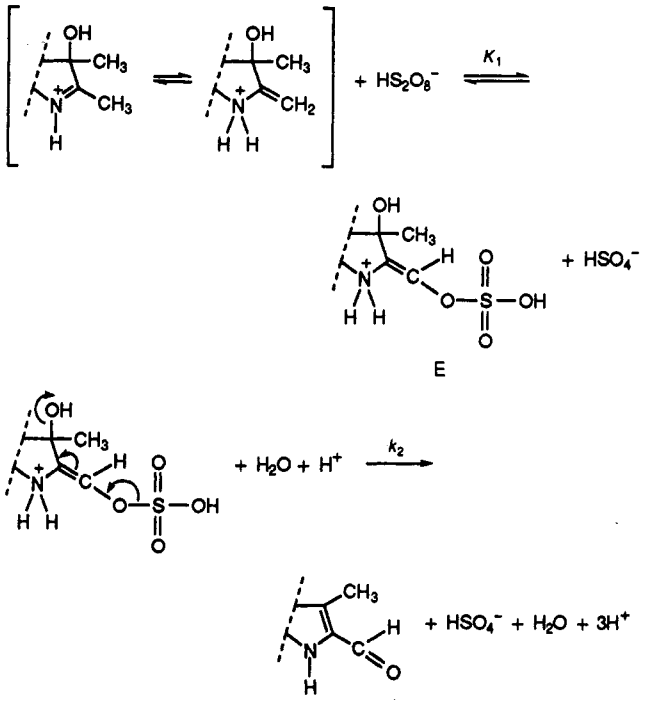
Discussion

The results obtained in the present paper indicate that under controlled acidic conditions, 2,3-dimethylindole suffers two peroxomonosulfate attacks to give 3-methylindole-2-carbaldehyde (**3**). We have previously postulated that electrophilic attack of PDS on 2,3-dimethylindole starts with substitution at C-3 atom of a sulfate group to give the indolenine intermediate.[1] This kind of intermediate was invoked on the basis of the known reactivity of indoles and the spectral changes observed in the reaction mixtures. The present experimental results give a direct evidence on the existence of such an intermediate for the similar reaction between 2,3-dimethylindole and PMS. Once the indolenine has been formed, a second PMS molecule is necessary to account for the formation of aldehyde **3**. Therefore, a new electrophilic attack instead of a rearrangement step has to be postulated for the second phase of the reaction.

As mentioned before, the formation of a product such of aldehyde **3** could be satisfactorily explained on the basis of the reaction of an enamine tautomer with an external agent. In fact, a key step on the general mechanism of the reactivity of indolenines, derived from 2,3-dialkylindoles, is the tautomerization of the indolenine to an exocyclic enamine.[6] Moreover, the presence of an enamine tautomer has even been postulated in the case of the dimethyl series,[6,7] although no alkyl group is present to stabilize the exocyclic double bond. In this tautomeric equilibrium, nucleophilic character has been assigned to enamines and electrophilic character to the carbon atom of imines.[7,8]

(15) Bascombe, K. N.; Bell, R. P. *J. Chem. Soc.* **1959**, 1096.

Scheme II



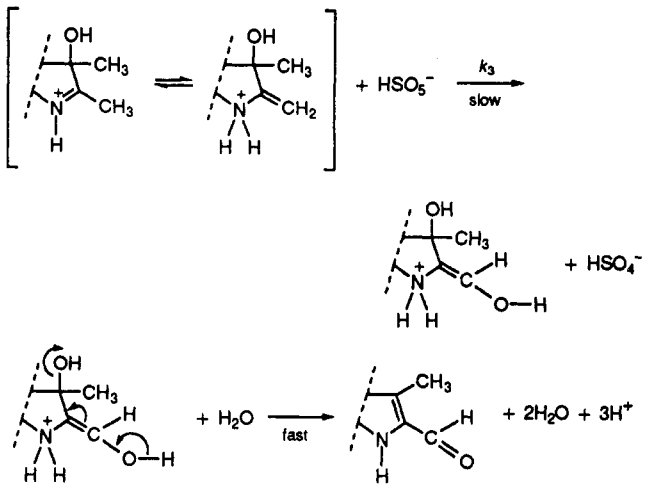
Thus, assuming that in the present case the acid media favors the short-lived enamine intermediate, an electrophilic attack of PMS on this enamine with displacement of substituent at C-3 atom, can be postulated for the second phase of the reaction. The same reasoning can be applied to the mechanism of **2a**–PDS reaction.

At this point, the following outstanding fact should be realized. The presence of a labile group at the C-3 atom is at least a necessary condition for the transformation of the indolenine into compound **3**. In favor of this assertion is the different reactivity pattern observed for the reaction of PMS or PDS with 1,3,3-trimethyl-2-methyleneindolenine and 2,3,3-trimethylindolenine. These indolenines only react with PDS in neutral form to give oxoindolic or dimeric products.[16] With PMS as the oxidizing agent, they react in both acid and neutral media, the indolic ring being apparently opened.[16] Thus, although an electrophilic attack of the peroxo anion could again be postulated, the lack of a labile group on the C-3 atom hinders the pathway for the aldehyde to be obtained as the final product.

The influence of acid concentration is a more puzzling question. Thus, while acidity does not make any influence on the first phase of the reactions, the increase of acid concentration increases the rate constant for **2a**–PDS reaction, but does not affect the **2a**–PMS reaction. The influence of acidity in the reactivity of these peroxo anions has often been explained on the basis of their protonation states.[9,17] However, in the range of acidity used in the present work PDS and PMS exist as the monoanions $HS_2O_8^-$ and HSO_5^-, respectively.[9,17] Therefore, if two electrophilic attacks of the peroxo anions are postulated, the influence of acidity cannot be accounted for the protonation of the oxidant, because it should be the same for the two steps of the mechanism. Thus, the only rational explanation for the acidity influence on the **2a**–PDS

(16) Unpublished results.
(17) Panda, R.; Panigrahi, A. K.; Patnaik, C.; Sahu, S. K.; Mahapatra, S. K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1363.

Scheme III



reaction is that it affects the step after the second peroxo anion attack. Therefore, the most probable mechanistic schemes for these reactions are those shown in Schemes II and III.

The rate law for the mechanism of Scheme II with application of the steady-state approximation to E is shown in eq 2

$$k''(\text{obs. 2}) = \frac{k_1k_2(\text{PDS})(\text{H}^+)}{k_{-1}(\text{HSO}_4^-) + k_1(\text{PDS}) + k_2(\text{H}^+)} \quad (2)$$

According to eq 2, and assuming that under our experimental conditions $k_{-1}(\text{HSO}_4^-) \ll k_1(\text{PDS}) + k_2(\text{H}^+)$, $[k''(\text{obs.2})]^{-1}$ exhibits a linear dependence on the reciprocal of proton activity with slope and intercept equal to $1/k_2$ and $1/k_1(\text{PDS})$, respectively. The linearity of this plot is shown in Figure 3. Also, if eq 2 holds up $[k''(\text{obs.2})]^{-1}$ versus $[(\text{PDS})]^{-1}$ should be linear with slope and intercept equal to $1/k_1$ and $1/k_2(\text{H}^+)$, respectively. The parameters obtained from these plots allow us to calculate the following mean values for the constants in Scheme II; $k_1 = (8.6 \pm 0.8)10^{-3}$ s^{-1} and $k_2 = (1.3 \pm 0.1)10^{-3}$ s^{-1}.

The rate law for the mechanism in Scheme III is given in eq 3:

$$k(\text{obs. 2}) \text{ or } k'(\text{obs. 2}) = k_3(\text{PMS}) \quad (3)$$

According to this equation, the plot of k(obs.2) or k'(obs.2) against PMS should be linear with zero intercept and slope equal to k_3. From these plots a medium value of $k_3 = 3.0 \pm 0.3$ M^{-1}s^{-1} can be obtained.

If we suppose the indolenine **2a** to be a right model compound for the intermediate **2b**, we can now summarize our interpretation of the mechanism of oxidation of 2,3-dimethylindole by peroxodisulfate and peroxomonosulfate anions in acid media.

(1) There is initially an electrophilic attack of the peroxo anion on the C-3 atom of the indole ring to give the indolenine intermediate.

(2) The second step is a new electrophilic attack of PDS or PMS on the enamine tautomer of the protonated indolenine. Hydrolysis of this new intermediate with displacement of the substituent at C-3 leads to the formation of 3-methylindole-2-carbaldehyde (**3**).

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