Kinetics and Mechanisms of the Oxidation Reactions of some 2,3-Dialkylindole Derivatives by Peroxodisulfate and Peroxomonosulfate Anions

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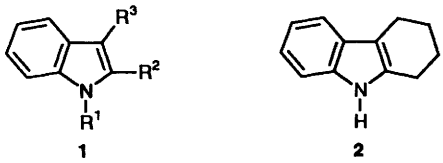
The kinetics and mechanisms of the oxidation of several 2,3-dialkylindoles, 2-methyl-3-ethyl-, **1b**; 2-ethyl-3-methyl-, **1c**; 1,2,3-trimethyl-, **1d**; 2-phenyl-3-methyl-, **1e** and 1,2,3,4-tetrahydrocarbazole **2** by peroxomonosulfate and peroxodisulfate anions have been investigated in sulfuric acid (0.1 mol dm^{-3} and 20% v/v methanol–water solutions. For each, the reaction pathway starts with the electrophilic attack of the peroxidic bond at the C-3 atom of the indole ring to give an indoleninic intermediate. The subsequent steps depend on the viability of the tautomerization of this indoleninic intermediate to an exocyclic enamine. Thus, in those cases where the short-lived enamine derivative is favoured, a second peroxoanion molecule attacks the exocyclic 2-methylene group to give a new intermediate, which, after hydrolysis, produces a 2-acylindole derivative. However, in those cases where the imine is favoured, there is not a second peroxoanion attack, the reaction products being the imine or an oxoindolic derivative.

We have recently studied[1] the mechanism of the oxidation of 2,3-dimethylindole, **1a**, to 3-methylindole-2-carbaldehyde, **3**, by peroxodisulfate (PDS) and peroxomonosulfate (PMS) anions in sulfuric acid media (0.1 mol dm^{-3}).[1,2] These studies threw new light on one interesting aspect of the mechanism of these oxidation reactions. Thus, as it is widely accepted for the electrophilic reactions of indoles, the reaction pathway started with the conversion of the indole to the 3*H*-indole intermediate, **4**.[3–5] However, the nature of the subsequent step of the mechanism was unknown. Thus, we knew only that an acid concentration ≥ 0.1 mol dm^{-3} was necessary to obtain the aldehyde **3**, because at sulfuric acid concentrations equal to or smaller than 0.01 mol dm^{-3} an oxoindolic derivative was formed. Therefore, to get a deeper insight into the reaction mechanism, we tried to isolate the reaction intermediates. While we were unable to isolate and identify without ambiguity the intermediate for the **1a**–PDS reaction, compound **4a**, we were successful in synthesizing and isolating the indolenine **4b**. This allowed us a straightforward comparison between the kinetic behaviour of the intermediate formed directly in the reaction media or obtained independently.

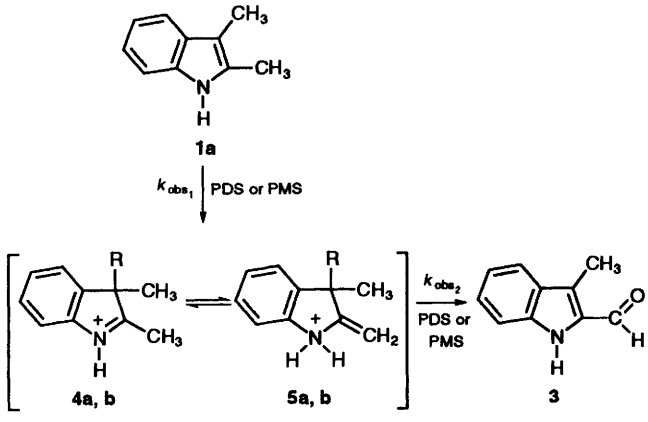


1 **2**

a $R^1 = H$, $R^2 = R^3 = CH_3$
b $R^1 = H$, $R^2 = CH_3$, $R^3 = C_2H_5$
c $R^1 = H$, $R^2 = C_2H_5$, $R^3 = CH_3$
d $R^1 = R^2 = R^3 = CH_3$
e $R^1 = H$, $R^2 = C_6H_5$, $R^3 = CH_3$

These measurements made evident a second peroxoanion attack giving a new intermediate. Thus, we postulated that in media of enough acidity for the indolenine, **4b**, to be protonated, ($pK_a = 2.47 \pm 0.08$),[1] its short-lived enamine tautomer, **5b**, was favoured. The second peroxoanion molecule attacked the exocyclic double bond of the enamine to give the new intermediate, which was further hydrolysed, with displacement of the substituent at C-3, to lead to compound **3**. This mechanism has been summarized in Scheme 1.

Therefore, as has already been proposed by other authors,[6–9] a key step in the mechanism of the oxidation of indole derivatives to 2-acylindoles seems to be the tautomerization of the indolenine intermediate to an exocyclic enamine.



1a

4a, b **5a, b** **3**

a $R = -OSO_3^-$
b $R = -OH$

Scheme 1

In spite of the significance of this step in the mechanism, there are only partial studies on the influence of different factors on it. Leete[10] has shown that 2,3-diethylindole oxidizes under acid-catalysis to furnish 2-acetyl-3-ethylindole but he was unable to obtain any 3-methylindole-2-carbaldehyde in the oxidation of compound **1a**. Nevertheless, Taylor[7] isolated about 5% of compound **3**, in the oxidation of indole **1a**. He explained this low yield with the assumption that the imine predominated over the enamine tautomer, since no alkyl group was present to stabilize the exocyclic double bond as in the case of 2,3-diethylindole. Moreover, Ying-Hsiueh Chen and Leete[9] have studied the oxidation of 2-benzyl-3-phenylindole, since in this compound an exocyclic double bond at the 2-position would be stabilized by the adjacent phenyl group. However, depending on the experimental conditions, they obtained the 2-acyl or the oxoindolic derivatives as the final products.

Therefore, as mentioned before, until now there is no definitive evidence of the factors influencing the imine–enamine tautomerism, and even of the necessity of such a tautomerism for the aldehyde to be obtained. For this reason, and to explore further the generality of this step in the mechanism of the oxidation of indole derivatives, we have decided to carry out a

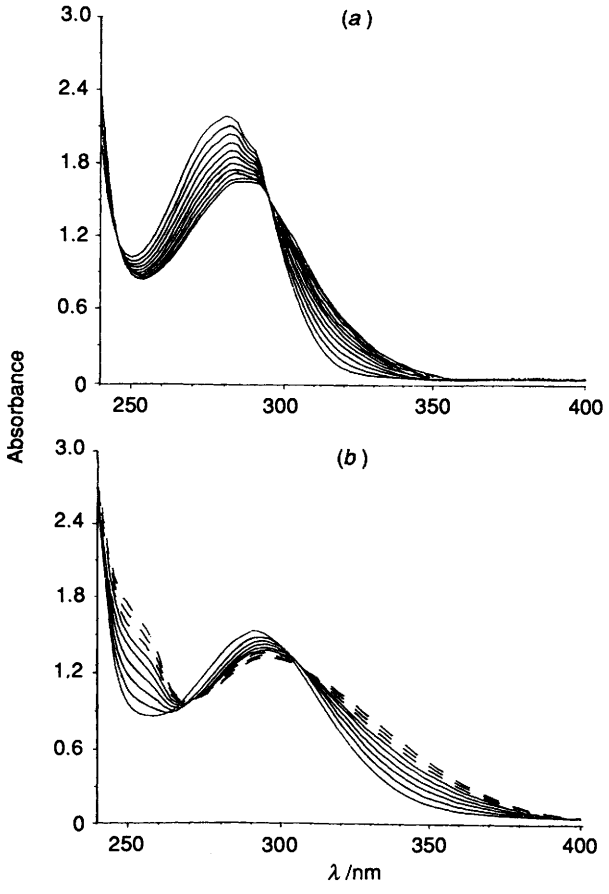


Fig. 1 Changes in UV spectra for the reaction mixture: [**1b**] = 2×10^{-4}, [PMS] = 2×10^{-3}, [H_2SO_4] = 0.1 mol dm^{-3} and 20% methanol–water. (*a*) At 5 second intervals. (*b*) At 1 min intervals and 1 min time delay.

systematic study in acidic media (H_2SO_4 0.1 mol dm^{-3}) on the influence of structural factors on this tautomerization. With this in mind, and assuming that the first step of the reaction is always the formation of the indoleninic intermediate, we have selected different substrates. Among them, ethyl substituted at C-2, compound **1c**, has been postulated to favour the short-lived enamine intermediate, while phenyl substitution at the same position, compound **1e**, should render impossible its formation. Moreover, the oxidation of indole **1d** should be of special interest because *N*-methyl substitution has been postulated to favour the enamine tautomer even in non-acidic media.[6] In fact, we have previously demonstrated by ^{13}C NMR spectroscopy that for a related indolenine, 1,2,3,3-tetramethyl-3*H*-indole, the neutral form, media of pH $\geq$ 8, is the enamine 1,3,3-trimethyl-2-methyleneindoline.[11]

Experimental

Compounds **1e** and **2** were used as received (Aldrich Química). Compounds **1b**, **1c** and **1d** were synthesized by the method described in the literature.[12,13] Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) and peroxodisulfate were purchased from Aldrich Química and Merck (AnalaR grade) respectively. The stock solutions of indole derivatives were prepared in methanol, stored in the dark and frequently renewed.

Kinetic experiments were always performed under pseudo-first-order conditions with an excess of PDS or PMS anions. The reaction rates of the first step with PDS and PMS were determined by monitoring the disappearance of the substrates at their maximum wavelengths. While PDS anions only allow

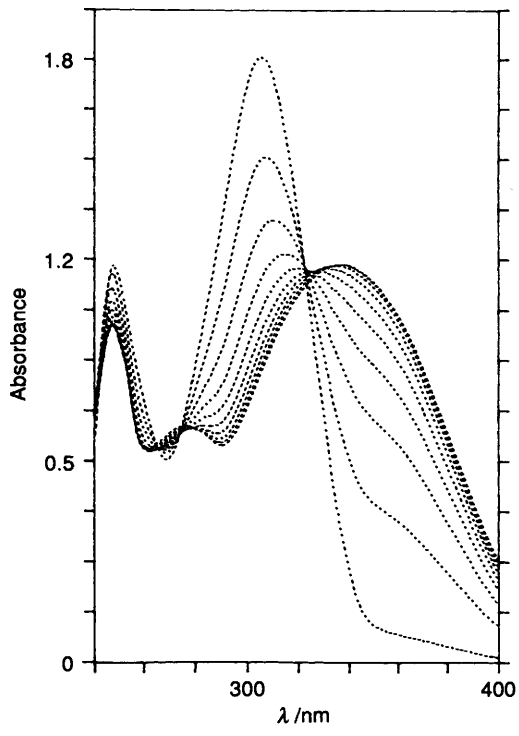


Fig. 2 Changes in UV spectra (at 5 min intervals) for the reaction mixture: [**1e**] = 2×10^{-4}, [PDS] = 0.07, [H_2SO_4] = 0.1 mol dm^{-3} and 20% methanol–water

a precise kinetic study on the first step of these oxidation reactions, PMS, due to its distinctive reactivity,[14,15] permits an independent and precise kinetic study on the two steps of the reaction mechanism, see Fig. 1. Thus, the rates of the second steps with PMS were followed by measurement of the absorbance increase at one of the maxima of the spectra of the corresponding 2-acyl derivative, 252 or 312 nm. Typically, the yields of indolenine or 2-acyl derivative formation were around 60–70% of the initial concentration of 2,3-dialkylindoles. When necessary, a rapid kinetic accessory was used. All the reactions were followed in a computer-interfaced spectrophotometer and the temperature was always maintained to within ±0.1 °C. Pseudo-first-order rate constants were obtained by a non-linear least-squares fitting of the absorbance time data as in previous work.[1]

Results

Typical reaction mixtures of the substrates and PDS in acid media were monitored by ultraviolet spectroscopy. In all the cases, except for compound **1c**, upon mixing the reactants there was an initial decrease of the absorbance at the maximum wavelength of the substrate, giving a spectrum corresponding to the well known absorption of the protonated indolenine chromophores: around 290 nm for derivatives **1b**, **d**[6,10] and **2**[16] and around 340 nm for an indole structurally related to indole **1e**.[17] A typical example of the formation of the indolenine intermediate is recorded in Fig. 2 for the indole **1e**–PDS reaction. These spectral changes were completely similar to those previously observed for the **1a**–PDS[2] reaction. Clear isosbestic points were always evident in the spectra.

Further, the spectral changes monitored depended on the structural characteristics of the substrates. Thus, for indoles **1b** and **1d** the spectra of the protonated indolenines disappeared and simultaneously an increase of the absorbance at about 312 nm, corresponding to the maximum wavelength of the 2-acylindoles, was observed. In the case of indole **1e**, its

Table 1 Pseudo-first-order rate constants ($k_{obs1}/10^{-3}$ s^{-1}) for the oxidation of compounds **1a–e** and **2** with PDS. Sulfuric acid 0.1 mol dm^{-3}

[PDS]/M	**1a**[a]	**1b**	**1c**	**1d**	**1e**	**2**
0.01	1.03	—	—	—	0.163	0.91
0.02	1.91	—	—	—	0.325	1.43
0.03	3.38	1.66	—	3.08	—	2.03
0.04	4.45	2.18	0.395	—	0.558	2.55
0.05	5.23	2.71	0.492	4.70	0.648	2.98
0.06	6.45	—	—	5.89	0.767	3.63
0.07	7.53	3.55	0.673	6.62	0.921	—
$k_1/10^{-2}$ dm^3 mol^{-1} s^{-1}	10.7 ± 0.5	4.7 ± 0.6	0.92 ± 0.07	9 ± 1	1.2 ± 0.1	5.4 ± 0.3
$k_{-1}/10^{-3}$ dm^3 mol^{-1} s^{-1}	—	—	—	—	—	5.1 ± 0.4

[a] Data taken from reference (2): k_1 are the values of the slopes of k_{obs1} *versus* [PDS] plots: k_{-1} is the value of the slope of k_{obs1} *versus* [SO_4^{2-}] plot.

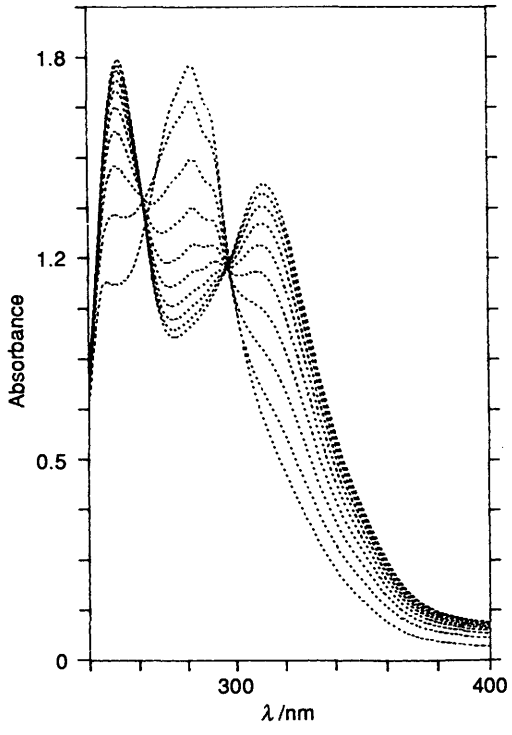


Fig. 3 Changes in UV spectra (at 5 min intervals) for the reaction mixture: [**1c**] = 2 × 10^{-4}, [PDS] = 0.07, [H_2SO_4] = 0.1 mol dm^{-3} and 20% methanol–water

protonated indolenine was rather stable and it did not react further, see Fig. 2. The spectrum of the indolenine of compound **2** was slowly transformed in the spectrum of an oxoindolic derivative, λ_{max} = 248 nm.[18]

Due to its higher reactivity, PMS is appropriate for an independent and precise kinetic study on the subsequent steps of the mechanism.[1] For this reason, and because we were only interested in the possible tautomerization of the imine intermediate to an exocyclic enamine and, therefore, in the second peroxoanion attack on the enamine double bond, we have only studied the reactivity with PMS of those derivatives which afford the 2-acylindole as the final product. As an example, the spectral changes for both steps of the reaction between **1b** and PMS are recorded in Fig. 1.

With respect to the behaviour of compound **1c**, the spectral changes were slightly different to those mentioned before. In this case, and for both peroxoanions, upon mixing the reactants, the disappearance of the indole was simultaneous with the appearance of the 2-acylindole derivative and the protonated indoleninic intermediate was not detected. Clear isosbestic points for this transformation were observed in the spectra, see Fig. 3.

Although we have not carried out a detailed kinetic study on the mechanism of these reactions in buffered media, pH around 4, it is worth making a comment on the influence of the protonation state of the indoleninic intermediate on the subsequent steps of the reaction. Thus, for the reactions with PDS in this medium, the indoleninic intermediates of compounds **1b** and **1c** were unprotonated (λ_{max} around 260 nm),[1] and they gave oxoindolic derivatives as the final products. In the cases of compounds **1e** and **2** their unprotonated indolenines (λ_{max} 320 nm and 265 nm respectively)[14,15] were fairly stable and they did not react further. However, in the oxidation of compound **1d** 1,3-dimethylindole-2-carbaldehyde was obtained even in media of pH up to 10.

The values of the rate constants for all the substrates at different PDS concentrations are recorded in Table 1. Likewise, Table 2 contains the rate constants for both steps, the disappearance of the indole k_{obs1} and the appearance of the 2-acyl derivative, k_{obs2} for the substrates **1b**, **c** and **d** at different PMS concentrations. For the sake of comparison, the rate constants for **1a**–PDS[2] and **1a**–PMS[1] reactions have also been included in these Tables.

In all the cases studied in this work, the measured rate constants at fixed PMS or PDS concentrations were the same over a range of substrate concentration. This is in agreement with first-order dependence on the concentration of the latter reactants.

As data in Tables 1 and 2 show, the experimental pseudo-first-order rate constants depend linearly on the concentration of PDS or PMS anions. In all the cases studied, except for compound **2**, the intercept at the origin was clearly zero. The values of the slopes of these plots, k_1, are recorded in these Tables. Due to the fact that intercept at zero PDS concentration for compound **2** was small and it could, therefore, be considered a negligible quantity, additional experiments were performed in order to be certain about its significance. Thus, for this system the influence of temperature was analysed. As displayed in Fig. 4, the plots were linear and the values of the intercept increased on increasing temperature. The existence of this intercept suggests that in this case, the peroxoanion attack is an equilibrium step, *i.e.*, k_{obs1} is described by eqn. (1).[19]

$$k_{obs1} = k_{-1}[SO_4^{2-}] + k_1[PDS] \quad (1)$$

To check this equation, experiments were carried out at fixed PDS concentration (4 × 10^{-2} mol dm^{-3}) and acid concentration ($HClO_4$ 0.1 mol dm^{-3}) but varying sulfate ion concentration (up to 0.3 mol dm^{-3}). The plot of k_{obs} *versus* sulfate concentration was also linear, Fig. 5, with slope and intercept equal to (5.1 ± 0.4) × 10^{-3} dm^3 mol^{-1} s^{-1} and (2.02 ± 0.08) × 10^{-3} s^{-1}

Table 2 Pseudo-first-order rate constants ($k_{obs1}/10^{-2}$ s^{-1} and $k_{obs2}/10^{-3}$ s^{-1}) for the oxidation of compounds **1a–d** by PMS. Sulfuric acid 0.1 mol dm^{-3}

	1a[a]		**1b**		**1c**[b]	**1d**	
[PMS]/10^{-3} mol dm^{-3}	k_{obs1}	k_{obs2}	k_{obs1}	k_{obs2}	$k_{obs1} = k_{obs2}$	k_{obs1}	k_{obs2}
0.5	—	—	—	—	2.00	—	—
1.0	2.79	2.87	1.23	3.50	3.68	2.71	1.97
1.25	—	—	—	—	4.36	—	—
1.5	4.05	4.02	1.83	5.25	5.18	3.86	3.00
2.0	5.45	5.80	—	—	—	4.95	4.05
2.5	6.79	6.93	—	—	—	5.96	4.86
3.0	7.83	8.40	4.10	10.71	—	—	—
k_1/dm^3 mol^{-1} s^{-1}	26 ± 2	3.0 ± 0.3	14 ± 3	3.6 ± 0.1	3.2 ± 0.3	21 ± 1	2.0 ± 0.2

[a] Taken from ref. (1): k_1 are the values of the slopes of k_{obs1} or k_{obs2} *versus* [PMS] plots. [b] $(k_{obs1} = k_{obs2})/10^{-3}$ s^{-1}.

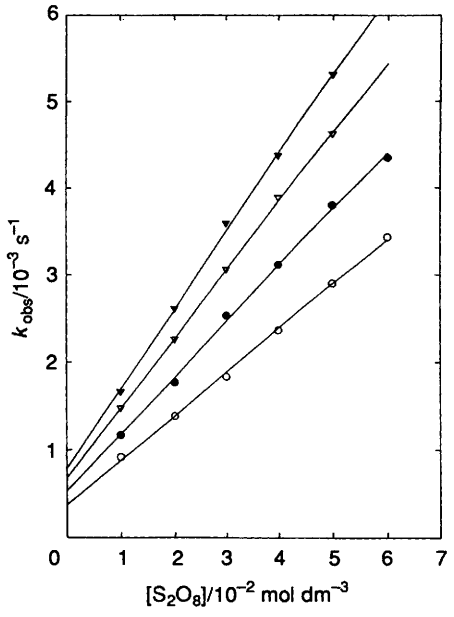


Fig. 4 Plots of k_{obs} *versus* peroxodisulfate concentration for compound **2** at different temperatures: [**2**] = 2 × 10^{-4}, [H_2SO_4] = 0.1 mol dm^{-3} and 20% v/v methanol–water

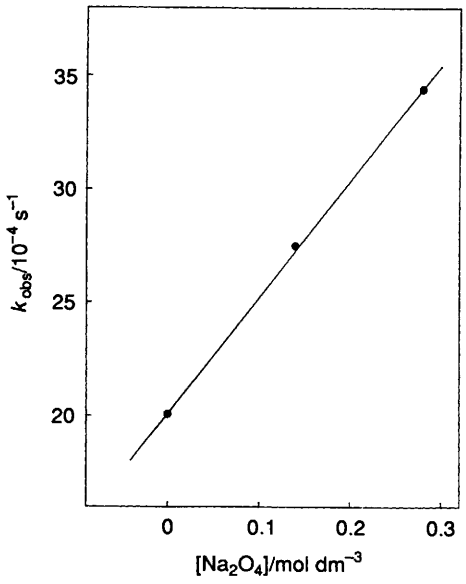


Fig. 5 Plot of k_{obs} *versus* sodium sulfate concentration for **2**–PDS reaction. [**2**] = 2 × 10^{-4}, [PDS] = 4 × 10^{-2}, [$HClO_4$] = 0.1 mol dm^{-3}, 298 K and 20% v/v methanol–water.

respectively. From this plot and the plots of k_{obs1} against [PDS] for compound **2**, the parameters in Table 1 have been obtained. Finally, we have also analysed the spectral changes observed upon mixing *N*-methyltetrahydrocarbazole with PDS. These changes were completely similar to those described for the reaction between **2** and PDS. That is, the 2-acyl derivative was not formed.

Discussion

The results obtained in the present paper indicate that, indoles **1b**, **c** and **d** follow exactly the same mechanism previously postulated for indole **1a**,[1,2] see Scheme 1. That is, they undergo, in sulfuric acid (0.1 mol dm^{-3}), two peroxoanion attacks to give the 2-acylindole derivative. However, there are some interesting differences in their kinetic behaviour that should be noted. As data in Tables 1 and 2 show, the presence of an ethyl group instead of a methyl group on the C-3 atom of the indole ring reduces, approximately, by half, the value of the observed rate constant for the first step of the reaction, while it does not apparently affect the second peroxoanion attack. When the ethyl group is located at the C-2 position of the indole ring, a more pronounced effect is observed. In this case, compound **1c**, the apparent rate constant for the first step of the reaction is one tenth the value of that for compound **1a**. This strong decrease of the rate for the first peroxoanion attack, together with the expected increase of the rate constant for the second step due to the presence of the ethyl group in the enamine tautomer, make the first step the rate controlling step. With respect to the reactivity of compound **1d**, data in Tables 1 and 2 show that its kinetic behaviour is completely similar to that observed for compound **1a**. That is, the presence of the methyl group at the nitrogen atom does not affect the reactivity of the substrate, neither in the first, nor in the second step of the reaction. Further, although, for simplicity, these data have not been included in the Tables, the reactivity of **1d** with PDS or PMS in aqueous and media of pH = 10, is completely similar to that observed in acid media. Thus, the slopes of the k_{obs} *versus* [PDS] plots are (9 ± 2) 10^{-2} dm^3 mol^{-1} s^{-1} in media of pH = 4 and (10 ± 2) 10^{-2} dm^3 mol^{-1} s^{-1} in media of pH = 10. Likewise, the slopes of the plots of the k_{obs1} and k_{obs2} against [PMS] are (21 ± 4) and (3 ± 0.4) dm^3 mol^{-1} s^{-1} in media of pH = 4 and (19 ± 3) and (3 ± 1) dm^3 mol^{-1} s^{-1} in pH = 10 media, respectively.

On the other hand, substitution of a methyl by a phenyl group at the C-2 position, indole **1e**, or inclusion of an exocyclic six-membered ring, compound **2**, decrease by a factor of ten or two, respectively, the values of the apparent rate constants for the first steps of these oxidation reactions. Interestingly, neither of these

substrates suffer a second PDS attack. Moreover, the protonated indolenine of compound **1e** does not react further and that of compound **2**, as we have already mentioned, reacts slowly to give an oxoindolic derivative. Possibly, this second step involves a nucleophilic attack of a solvent molecule on the carbon atom of the imine.[20] Thus, as expected, the presence of the phenyl group at the C-2 position, blocks the imine–enamine tautomerization and, therefore, the pathway to the formation of a 2-acylindole derivative as the oxidation product. Also, in the case of compound **2**, the exocyclic six membered ring apparently hinders the stabilization of the planar enaminic derivative even, as we have already mentioned, after methylation of the nitrogen atom.

Therefore, taking into account that indole **1e**, which renders impossible the enamine intermediate formation, does not oxidize to the 2-acyl derivative and that indole **1d**, which has been demonstrated to be in the enaminic form in basic media, always gives the aldehyde as the oxidation product, we can conclude that the presence of the enaminic tautomer is essential to account for the formation of 2-acylindole derivatives.

The factors influencing the tautomerization of the indolenine to its enaminic derivative, are more complicated to summarize. The acidity of the media is an important but not a definitive factor, as is clearly demonstrated by the comparison of the behaviour of indoles **1a–d** with compounds **1e** and **2**. Moreover, protonation of the indoleninic intermediate is not necessary in the case of a substrate such as compound **1d**. Further, the fact that *N*-methylation favours the enaminic tautomer formation is not a general rule, since as demonstrated for compound **2**, its effect also depends on the structure of the substrate. Therefore, we can only conclude that both factors together, *i.e.* protonation state of the indolenine and structural characteristics of the substrates, should be taken into account in order to postulate the formation of the enaminic intermediate as one of the steps in the mechanism of the oxidation reactions of indole derivatives.

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