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Dedicated to the memory of Professor Nicholas Alexandrou

In methanol-water mixtures containing sodium or potassium hydroxide (up to 2.00M) the demethoxylation of 9-methoxyacridine to 9-acridone is of first order in both the free form of 9-methoxyacridine and the hydroxyl ion. The rate of the reaction is increased with an increase in the concentration of water. Sodium perchlorate has a small retarding effect on the reaction. In methanol-water mixtures containing perchloric or hydrochloric acid (up to 3.45M) the demethoxylation is of first order with respect to the protonated form of 9-methoxyacridine. The rate of the reaction decreases with an increase in the concentration of the acid or of sodium perchlorate, but when the concentration of water is increased (≈ 1.7 to 50M) and that of the acid is not changed, it reaches a maximum value in mixtures containing 8 to 10M-water. The dechlorination of 9-chloroacridine to 9-methoxyacridine in methanol containing sodium hydroxide or methoxide (up to 0.31M) is of first order in both the 9-chloroacridine and the hydroxyl or methoxyl ions.

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In view of the observation that the rate of the deamination of 9-aminoacridines in aqueous alkaline solutions is independent whilst that of 2- and 4-aminopyrimidines is dependent on the concentration of the hydroxyl ions [1], the kinetics of the demethoxylation of 9-methoxyacridine and of the dechlorination of 9-chloroacridine in hydroxylic solvents were examined because these compounds contain in the 9-position substituents which are less basic, but better leaving than the amino group [2].

The hydrolysis of 9-methoxyacridine has been examined in buffered aqueous solutions from pH 0 to 10 and it has been suggested that the protonated form of 9-methoxyacridine is the reactive species at all pH values [3]. However, the effect of high concentrations of alkali, acid or neutral salts on the rate of the reaction has not been examined. The hydrolysis of 9-chloroacridine has been examined in aqueous acid solutions [4], but not in alcoholic solutions containing alkali.

Results and Discussion.**Alkaline Solutions.****9-Methoxyacridine.**

The demethoxylation of 9-methoxyacridine ($pK_a \approx 7$ at 20°) [5] to 9-acridone ($pK_a -0.32$ at 20°) [5] in methanol-water mixtures containing 0.10-2.00M-sodium or potassium hydroxide follows rate expression (1) and any increase in the initial concentration of 9-methoxyacridine from 0.5×10^{-4} to $1.5 \times 10^{-4}M$ failed to alter the values of the first order rate coefficients k_1 .

$$\text{Rate} = k_1[9\text{-Methoxyacridine}] \quad (1)$$

The rate of the reaction, which remains unaffected when sodium hydroxide is replaced by potassium hydroxide (Table 1), increases with an increase in the concentration of water (Table 1 and Figure 1) or with an increase in

Table 1
Demethoxylation of 9-Methoxyacridine at 45.0° in Methanol-water
Mixtures Containing Various Concentrations of Sodium or Potassium
Hydroxide

[NaOH]/M	[KOH]/M	[H ₂ O]/M	[MeOH]/M	10 ⁶ k ₁ /s ⁻¹
		($\approx 90\%$)		
0.10	—	49.9	2.46	12.7 $\pm$ 0.3
0.30	—	49.8	2.46	35.1 $\pm$ 1.0
0.50	—	49.8	2.46	53.2 $\pm$ 1.2
1.00	—	49.4	2.46	112 $\pm$ 3
1.50	—	49.2	2.46	183 $\pm$ 4
2.00	—	48.8	2.46	244 $\pm$ 6
		($\approx 50\%$)		
—	0.10	27.7	12.3	2.34 $\pm$ 0.07
—	0.50	27.5	12.3	9.94 $\pm$ 0.24
—	1.00	27.3	12.3	20.3 $\pm$ 0.4
—	1.50	27.1	12.3	31.4 $\pm$ 1.0
0.50	—	27.4	12.5	9.83 $\pm$ 0.31
1.00	—	27.4	12.5	19.8 $\pm$ 0.5

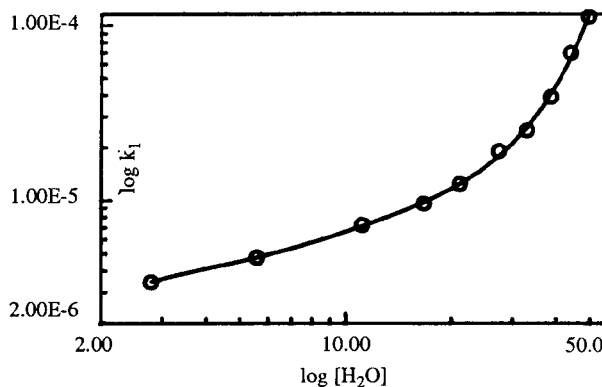


Figure 1. Demethoxylation of 9-methoxyacridine at 45.0° in methanol-water mixtures containing 1.00M-sodium hydroxide. Variation of reaction rate with the concentration of water in the mixtures.

the concentration of the hydroxyl ion (Table 1).

The reaction was studied in methanol-water mixtures because 9-methoxyacridine has a very low solubility in water. In such mixtures, in which the concentration of water is not significantly changed (Table 1), the dependence of the rate of the reaction on the concentration of alkali is rectilinear, since a plot of $\log k_1$ against $\log[\text{MOH}]$, where $M = \text{Na}$ or K , gave straight lines with a slope of unity. For example, at 45.0° and in methanol-water mixtures ($\approx 50\%$ water) containing potassium hydroxide or in mixtures ($\approx 90\%$ water) containing sodium hydroxide, the slopes of the straight lines were 0.96 and 0.98, respectively (Table 1).

These results are in contrast to those of the deamination of 9-aminoacridines in aqueous alkaline solutions since the deamination was found not to be accelerated by an increase in the concentration of alkali [1].

$$\text{Rate} = k_2[\text{Free 9-Methoxyacridine}][\text{MOH}] \quad (2)$$

The above results (Table 1) show that $k_1 \propto [\text{MOH}]$ and therefore equation (1) can be rewritten as equation (2) because 9-methoxyacridine is completely in the free form under the present conditions. This indicates that the demethoxylation of 9-methoxyacridine in methanol-water mixtures containing alkali is a nucleophilic reaction which in the slow step involves the attack of the hydroxyl ion on the free 9-methoxyacridine (Scheme 1). In addition,

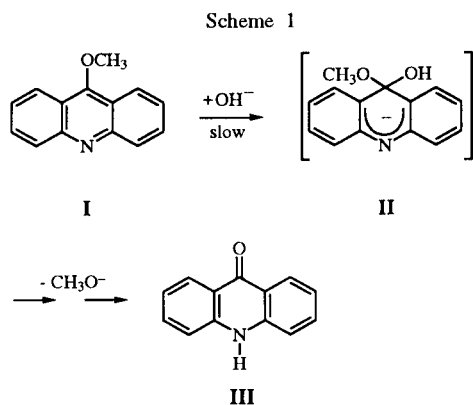


Table 2

Demethoxylation of 9-Methoxyacridine at Various Temperatures in Methanol-water Mixtures Containing 1.00M-Sodium Hydroxide

Temp/ $^\circ\text{C}$	Methanol-water	
	22.1M-5.54M $10^6 k_1/\text{s}^{-1}$	2.46M-49.4M $10^5 k_1/\text{s}^{-1}$
35.0	—	4.53 ± 0.10
40.0	3.11 ± 0.08	6.87 ± 0.15
45.0	4.80 ± 0.12	11.2 ± 0.3
50.0	9.00 ± 0.24	16.9 ± 0.3
55.0	17.7 ± 0.5	26.8 ± 0.5
60.0	28.7 ± 0.6	—
$E_a/\text{kJ mol}^{-1}$	100	75
$-\Delta S^\ddagger/\text{J mol}^{-1}\text{K}^{-1}$	42	94

tion, the values of $\Delta S^\ddagger$ are negative and together with the values of E_a they are both consistent with those for nucleophilic reactions [6] (Table 2). It is unlikely that the protonated form of 9-methoxyacridine formed in a slow step is the reactive species as proposed earlier [3], since in that case an increase in the hydroxide concentration should have caused a decrease in the rate of the reaction instead of a rectilinear increase which is actually observed (Table 1).

In methanol-water mixtures in which the concentration of sodium hydroxide (1.00M) is not changed, the dependence of the rate of the reaction on the concentration of water (from $\approx 2.7M$ to $49.5M$) is not rectilinear since at all temperatures examined a plot of $\log k_1$ against $\log[\text{H}_2\text{O}]$ is a curve with a rising slope (Figure 1). When the concentration of water is less than $\approx 16M$ the curve has an approximate slope of 0.5, *i.e.* much less than unity (Figure 1), indicating that water, unlike the hydroxyl ion [equation (2)], does not participate in the demethoxylation as a nucleophile.

Although water is more polar than methanol [7] its accelerating effect on the rate of demethoxylation cannot be due to an increase in the polarity of the medium since the addition of neutral salts, such as sodium perchlorate, causes only a small decrease, instead of an increase, in the rate of the reaction. For example, in methanol-water mixtures containing 22.8M-water and 0.50M-sodium hydroxide the value of k_1 for the demethoxylation at 40.0° is $3.42 \times 10^{-6} \text{ sec}^{-1}$, whilst in similar mixtures and in the presence of 2.0M-sodium perchlorate the value of k_1 is $2.91 \times 10^{-6} \text{ sec}^{-1}$, *i.e.* lower by $\approx 15\%$. It is, therefore, more likely that the increase in the rate of the reaction due to the increase in the concentration of water is the result of a specific solvation effect through hydrogen bonding between the hydroxylic solvent and the ring nitrogen of the substrate. Since water is more acidic than methanol [8], this effect becomes more pronounced as the water content of the reaction mixtures is increased (Figure 1).

The increase in the concentration of water in the reaction mixtures causes a substantial decrease in the values of E_a and $\Delta S^\ddagger$ (Table 2). Thus an increase in the water content from 5.54M ($\approx 10\%$) to 49.4M ($\approx 90\%$) caused a decrease in the value of E_a by 25 kJ mol^{-1} and a decrease in the value of $\Delta S^\ddagger$ by $52 \text{ J mol}^{-1}\text{K}^{-1}$ resulting in an increase in the rate of demethoxylation since the decrease in the value of E_a is more dominant (Table 2).

The reaction scheme (Scheme 1) proposed for the demethoxylation of the free form of 9-methoxyacridine in alkaline solutions is consistent with the present results. Thus, the small negative salt effect of sodium perchlorate on the rate of the reaction must be due to the negative charge of the hydroxyl ion being more diffuse in the transition state II. Such an effect is consistent with those observed in reactions between an ion and a neutral mole-

cule [9a]. Also the increase in the negative charge on the ring nitrogen in the transition state **II** due to the incoming hydroxyl ion, enhances a specific solvation of the substrate through hydrogen bonding between the hydroxylic solvent and the ring nitrogen. The reaction is therefore much faster when the water content of the mixtures is increased because stronger solvation by water makes carbon-9 more susceptible to nucleophilic attack as shown by the substantial lowering in the E_a values (Table 2). Also in mixtures containing more water the transition state **II** is expected to be tighter than in the mixtures containing less water resulting in a substantial lowering in the $\Delta S^\ddagger$ values (Table 2).

9-Chloroacridine.

The dechlorination of 9-chloroacridine in methanol containing 0.05-0.30*M*-sodium hydroxide takes place with the formation of 9-methoxyacridine presumably because of the prior formation of methoxyl ions. The reaction follows rate expression (3). In methanol containing 0.05-0.31*M*-sodium methoxide the dechlorination to 9-methoxyacridine also follows rate expression (3).

$$\text{Rate} = k_1[9\text{-Chloroacridine}] \quad (3)$$

$$\text{Rate} = k_2[9\text{-Chloroacridine}][\text{NaOR}] \quad (4)$$

The values of k_1 , which were almost identical in both reaction media (Table 3), were independent of the initial concentration of 9-chloroacridine which was varied from 1.0×10^{-4} to $4.0 \times 10^{-4}M$. The rate of the reaction increased with an increase in the concentration of alkali (Table 3) and at all temperatures examined the plots of $\log k_1$ against $\log[\text{NaOR}]$, where $R = \text{H}$ or CH_3 , gave straight lines with slopes of unity. For example at 45.0° the slopes were 1.03 or 1.02, respectively. Therefore $k_1 \propto [\text{NaOR}]$ and equation (3) can be rewritten as equation (4).

Therefore it can be concluded that the dechlorination is a nucleophilic reaction and that the slow step involves the attack of 9-chloroacridine by the methoxyl ions in a way similar to that shown for the reaction of 9-methoxyacri-

dine with the hydroxyl ions (Scheme 1). The values of E_a and $\Delta S^\ddagger$ which are negative (Table 3) are consistent [6] with this deduction.

The present results show that although 9-methoxy- and 9-chloro-acridine have better leaving groups [2] than 9-aminoacridines in the 9-position, their demethoxylation or dechlorination respectively in alkaline solutions involve strong nucleophiles in the slow step (hydroxyl or methoxyl ions). However in the case of the deamination of 9-aminoacridines a different mechanism must be involved, since the rate of the reaction in this case is not dependent on the concentration of the hydroxyl ions [1].

Acid Solutions.

9-Methoxyacridine.

In methanol-water mixtures containing perchloric (up to 0.90*M*) or hydrochloric acid (up to 3.45*M*) the demethoxylation of 9-methoxyacridine follows rate expression (1) and any increase in the initial concentration of 9-methoxyacridine from 0.5×10^{-4} to $2.0 \times 10^{-4}M$ failed to alter the first order rate coefficients k_1 . An increase in the concentration of water in the reaction mixtures from $\approx 1.7M$ to 50*M* causes initially an increase and then a decrease in the rate of the reaction, which reaches a maximum value when the water concentration is between 8 and 10*M* (Figure 2).

In addition, the rate of demethoxylation is decreased as the concentration of the acid is increased. Thus, when the concentration of perchloric acid is increased from 0.45 to 0.90*M* the values of k_1 at 25.0° are decreased by about 2.5 times (Figure 2). When the concentration of hydrochloric acid is increased from 0.39 to 3.45*M* the values of k_1 at 20.0° are decreased by about 6 times (Table 4) instead of being increased, as expected from Figure 2, since in this case the concentration of water is decreased (Table 4).

This retarding effect is attributed to a negative medium

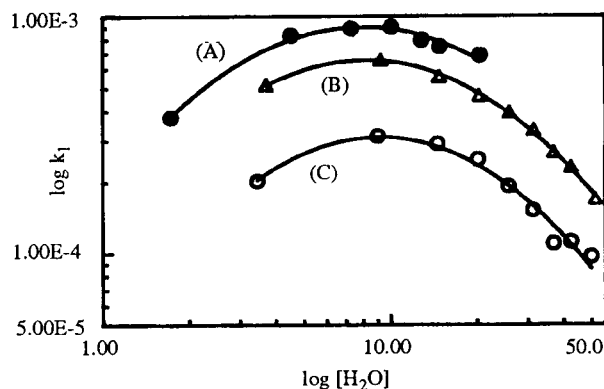


Figure 2. Demethoxylation of 9-methoxyacridine at 25.0° in methanol-water mixtures containing 1.34*M*-hydrochloric (A), 0.45*M*-perchloric (B) and 0.90*M*-perchloric acid (C). Variation of reaction rate with the concentration of water in the mixtures.

Table 3

Dechlorination of 9-Chloroacridine to 9-Methoxyacridine at 45.0° in Methanol Containing Various Concentrations of Sodium Hydroxide or Methoxide

[NaOH]/ <i>M</i>	[NaOCH ₃]/ <i>M</i>	$10^4 k_1/s^{-1}$	$E_a/kJ\ mol^{-1}$	$-\Delta S^\ddagger/Jmol^{-1}K^{-1}$ (35.0 - 50.0°)
0.05	—	0.722 ± 0.026	—	—
—	0.05	0.739 ± 0.031	—	—
0.07	—	0.939 ± 0.019	—	—
0.11	—	1.60 ± 0.03	—	—
—	0.10	1.53 ± 0.04	72	98
0.15	—	2.25 ± 0.06	76	85
—	0.15	2.21 ± 0.04	—	—
0.20	—	3.14 ± 0.06	75	87
—	0.23	3.62 ± 0.08	—	—
0.30	—	4.20 ± 0.08	—	—
—	0.31	4.57 ± 0.10	71	96

effect of the acid, which is greater in the case of perchloric acid; for example, the values of k_1 at 25.0° in 0.90M-perchloric acid are about 3 times smaller than those obtained in 1.34M-hydrochloric acid (Figure 2). The negative medium effect of the acid is confirmed by the observation that the addition of 0.20-1.00M-sodium perchlorate in methanol-water mixtures containing 0.05M-perchloric acid caused a decrease in the values of k_1 by about 2 times (Table 5) although, according to the results in Figure 2, an increase in these values should have been expected since the concentration of water is decreased due to the addition of the salt (Table 5). The negative medium effect on the demethoxylation is consistent with that observed for a reaction [9a] in which one of the species involved is charged, *i.e.* 9-methoxyacridinium ion, and the other is neutral, *i.e.* water, according to equation (5), since under the present conditions 9-methoxyacridine is completely protonated.

$$\text{Rate} = k_2[\text{9-Methoxyacridinium ion}][\text{H}_2\text{O}] \quad (5)$$

From equations (1) and (5) it should follow that $k_1 = k_2[\text{H}_2\text{O}]$, *i.e.* a plot of $\log k_1$ against $\log[\text{H}_2\text{O}]$ should be a straight line with a slope of unity. However, the relationship obtained experimentally is a curve approaching a parabola (Figure 2) which is the result of two opposing effects: one due to the increase in the concentration of water, as the nucleophile [equation (5)], causing an increase in the values of k_1 [equation (1)], and the other due to an increase in the polarity of the reaction mixtures, since water is more polar than methanol [7], causing an increase in the negative medium effect and hence a decrease in the values of k_1 . These two opposing effects presumably become equal in methanol-water mixtures

Table 4

Demethoxylation of 9-Methoxyacridine at 20.0° in Methanol-water Mixtures Containing Various Concentrations of Hydrochloric Acid

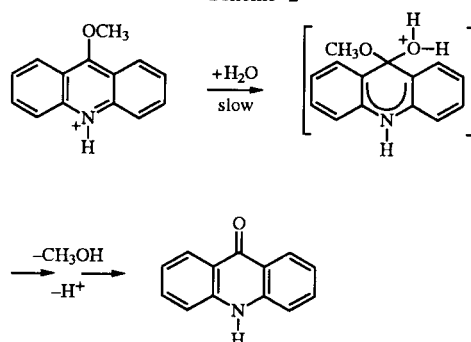
[HCl]/M	[H ₂ O]/M	[MeOH]/M	10 ⁵ k_1 /s ⁻¹
0.39	49.8	2.46	15.2 ± 0.4
0.77	49.3	2.46	13.5 ± 0.3
1.16	48.5	2.42	10.3 ± 0.2
1.93	47.8	2.54	6.83 ± 0.17
2.70	46.8	2.55	4.21 ± 0.09
3.45	46.1	2.59	2.56 ± 0.06

Table 5

Demethoxylation of 9-Methoxyacridine at 20.0° in Methanol-water Mixtures Containing 0.05M-Perchloric Acid and Various Concentrations of Sodium Perchlorate

[NaClO ₄]/M	[H ₂ O]/M	[MeOH]/M	10 ⁵ k_1 /s ⁻¹
0.20	16.0	17.2	4.36 ± 0.09
0.40	15.5	17.2	3.40 ± 0.07
0.60	15.0	17.2	3.03 ± 0.07
0.80	14.5	17.2	2.36 ± 0.06
1.00	14.0	17.2	1.97 ± 0.06

Scheme 2



containing water between 8 and 10M. It is then considered that the slow step of the reaction involves the attack of water, as the nucleophile, on the protonated form of 9-methoxyacridine (Scheme 2), which is more reactive than the free form (Figures 1 and 2).

It is unlikely that the slow step of the demethoxylation in acid solutions involves the loss of a proton from the complex formed after the addition of a molecule of water to the protonated 9-methoxyacridine, as proposed earlier [3], because if that were the case there should not have been an increase and then a decrease in the values of k_1 with an increase in the concentration of water (Figure 2).

EXPERIMENTAL

The uv-visible spectra were recorded and measured on a SP1800 Unicam or a DMS-90 Varian Spectrophotometer and, when necessary, checked on a Beckman DU-65 Spectrophotometer.

Materials.

Methanol (Merck, P.A.) was further purified by treatment with magnesium (Merck) and then by distillation [10]. Sodium and potassium hydroxide (Merck, P.A.) were used to make up aqueous or methanolic stock solutions (1.0, 2.0 and 5.0M) by washing (decantation) the solid alkali (Merck, P.A.) several times with the appropriate solvent prior to dissolution and then standardizing the solutions obtained against hydrochloric acid (AnalaR). Methanolic sodium methoxide solutions were prepared by dissolving sodium in methanol after washing the metal several times with petroleum ether (bp 60-80°) and then with methanol and standardizing the final solutions against hydrochloric acid (AnalaR). Hydrochloric acid (Merck, pro analysi, 25 or 37%) and perchloric acid (Fluka, puriss, 60 or 70%) were diluted and molarities of stock solutions were determined by titration against standard alkali solutions (Merck titrisol). Sodium perchlorate (Merck, P.A.) was dried at 150° for 6 hours before use.

(a) 9-Methoxyacridine.

Prepared from 9-chloroacridine and sodium methoxide in methanol [11a].

(b) 9-Chloracridine.

This compound was prepared from diphenylamine-2-carboxylic acid [11b].

Both products were dissolved in benzene, treated with charcoal and filtered at room temperature. After evaporation of the solvent they were sublimed twice at 60° and 80° respectively and 0.1 Torr.

Anal. (a). Calcd. for $C_{14}H_{11}ON$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.44; H, 5.38; N, 6.72.

Anal. (b). Calcd. for $C_{13}H_8NCl$: C, 73.08; H, 3.77; N, 6.56. Found: C, 73.31; H, 3.68; N, 6.67.

Kinetics.

Alkaline Solutions.

(a) 9-Methoxyacridine.

Runs were carried out by using standard solutions (10.0M or 20.0M) of water in methanol, 9-methoxyacridine in methanol and the appropriate sodium hydroxide solutions. Molarities of all components were calculated from the weights of the required volumes of their standard solutions and from the weight of the solvent used to prepare known volumes of the reaction mixtures. The reaction was followed either by extracting samples (2.0 or 3.0 ml) at timed intervals from the reaction mixtures kept at the required temperature and, if necessary, diluting with an equal volume of water, or by placing portions of the reaction mixtures in thermostated 10 mm silica cells. Spectra of the final solutions were recorded and the decrease in the absorbance was read at 354 nm. Small variations in the values of the extinction coefficients (ϵ), due to the variations in the composition of the reaction mixtures were observed. The values of ϵ for 9-methoxy- and 9-hydroxy-acridine in methanol at 354 nm are 8.02×10^3 and $2.30 \times 10^3 \text{ l mol}^{-1}\text{cm}^{-1}$ respectively.

(b) 9-Chloroacridine.

Runs were carried out by mixing in volumetric flasks (20, 25 or 50 ml) the required volumes of standard solutions of 9-chloroacridine and of sodium hydroxide or methoxide in methanol. The spectra of the reaction mixtures were recorded at regular timed intervals after placing portions of the reaction mixtures in thermostated 10 mm silica cells. Absorbances were read at 360 nm at which the absorbance of 9-methoxyacridine was substantial ($\epsilon = 5.37 \times 10^3 \text{ l mol}^{-1}\text{cm}^{-1}$) when compared to that of 9-chloroacridine ($\epsilon = 9.95 \times 10^3 \text{ l mol}^{-1}\text{cm}^{-1}$).

Acid Solutions.

9-Methoxyacridine.

Runs were carried out by mixing appropriate volumes of water,

methanol, standardized perchloric or hydrochloric acid and methanolic 9-methoxyacridine solutions and making up to the mark in 10 ml volumetric flasks. Molarities of all components were calculated from the weights of their volumes. Portions of the reactions mixtures were placed in 10 mm thermostated silica cells and the decrease in the absorbance was measured at 349 nm. Small variations in the values of ϵ , due to variations in the composition of the reaction mixtures, were observed. For example, in mixtures containing 1.16M-hydrochloric acid and 48.6M-water the values of ϵ for 9-methoxyacridinium ion was 10.3×10^3 and for 9-hydroxyacridine was $2.12 \times 10^3 \text{ l mol}^{-1}\text{cm}^{-1}$.

Calculations.

Rate coefficients (within $\pm 5\%$ error) were determined from the usual first order rate equation for irreversible reactions [9b]. Absorbances were used directly after applying the necessary corrections because of the absorbance of 9-hydroxy- or 9-methoxyacridine, by using equation (6), where A_1 is the initial absorbance, A_2 the absorbance at time t and A_3 the absorbance at infinity time of the reaction mixtures.

$$A = [A_1(A_2 - A_3)/(A_1 - A_3)] \quad (6)$$

Values of E_a were determined from the least squares slopes of the appropriate Arrhenius plots from which the values of $\Delta S^\ddagger$ were estimated [6]. The method of least squares was always adopted when plotting experimental values. Beer-Lambert's law was obeyed in all cases. Good first-order behaviour was found over two or three half-lives.

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