HETEROCYCLES, Vol.9, No.10, 1978

REACTIONS AT C-9 POSITION OF ACRIDINE DERIVATIVES. PART XVIII[1].

ON THE MECHANISM OF HYDROLYSIS (SOLVOLYSIS) OF 9-CHLOROACRIDINE IN AQUEOUS ACETIC ACID

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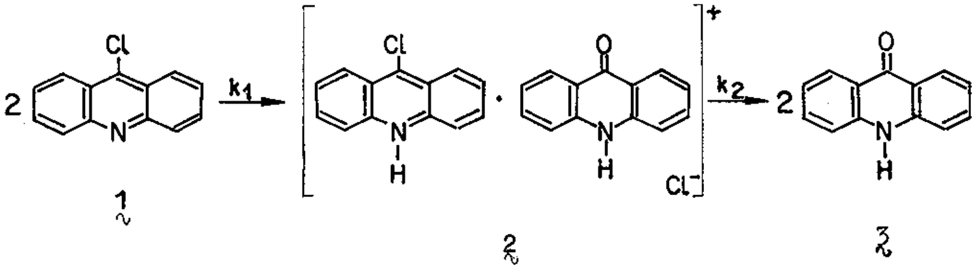
The kinetics of solvolysis of 9-chloroacridine (1) in 80 % aqueous acetic acid and its hydrolysis in aqueous hydrochloric acid of pH from 0 to 3 have been studied. The reaction occurs in two distinct stages in acetic acid but follows pseudo-first-order kinetics with respect to 1 in hydrochloric acid. No traces of the π-complex (2) suggested for the former case are observed in the u.v. spectra, and reaction rate constant for the hydrolysis in hydrochloric acid are identical with those of the second step of the consecutive reaction in acetic acid at the same concentration of 1. This implies a mechanism with 9-chloroacridine hydrochloride (5) as an intermediate in the solvolysis process. Hydrogen bonded compound 4 is discussed as a possible intermediate in most

nucleophilic substitution reactions at 9-position of **1**.

9-Chloroacridine (**1**) and its derivatives are still the most widely used intermediates in the syntheses of numerous biologically active acridine derivatives[2] due to the facile replacement of the chlorine atom[3]. 9-Chloroacridines are often extremely sensitive to acid hydrolysis and even a pure sample suffers autocatalyzed decomposition to the corresponding 9-acridanone derivatives.

Magidson and Grigorovski[4] investigated the kinetics of hydrolysis in 50 % aqueous acetic acid employing titration of chloride anions formed in the process and found the reaction to be of pseudo-first-order with respect to the substrate up to its 50 or 60 % conversion. Ledóchowski[5,6] has extensively extended the investigations varying concentration of both acetic acid and 9-chloroacridine and following the reaction up to over 80 % conversion. He has pointed out that the hydrolysis occurs in a pseudo-first-order two-step consecutive reaction according to the following scheme.[6]



The intermediate addition compound, a hydrate of 2, was isolated.[6] Moreover, such compounds which were believed to precipitate from concentrated solutions of 1[6], had been described earlier by Drozdov and Leznova[7] when 10 % aqueous hydrochloric acid was used as a hydrolysis medium.[8]

Aqueous acetic acid was chosen as a reaction medium owing to its unique feature of dissolving 9-acridanone (3). More recently, however, Inoue et al.[9] have described the reaction of carboxylic acids with 9-chloroacridine. Therefore it was of interest to re-investigate the hydrolysis reaction spectrophotometrically.

The solvolytic reaction of 1 in 80 % aqueous acetic acid was carried out under the same conditions as reported previously[5,6] by monitoring spectrophotometrically. An example of such a spectrum set obtained is shown in Figure 1. The present results were almost identical with those described earlier.[5,6]

The solvolysis followed a two-step consecutive reaction kinetics, though the rate constant differed more significantly at the lowest and at the highest values of reaction percentage.

The hydrolysis of 1 was performed in aqueous hydrochloric acid of pH 0, 0.5, 1, 1.5, 2, 2.5, and 3 and these results were summarized in Table 1. The decrease of the 9-chloroacridine absorption at 359.6 nm as well as increase of the 9-acridanone absorption at 382.5 nm were found to follow a first-order law. Standard deviations in rate constant ranged from 5×10^{-7} s^{-1} at 40°C to 60×10^{-7} s^{-1} at 70°C.

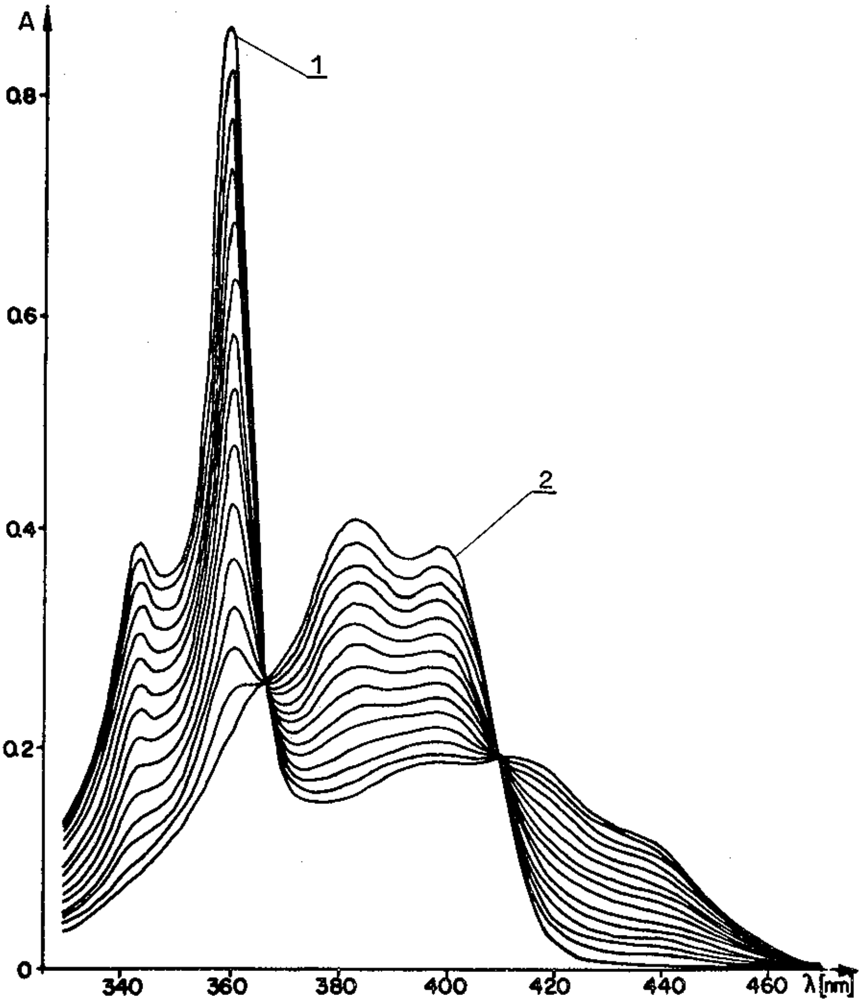


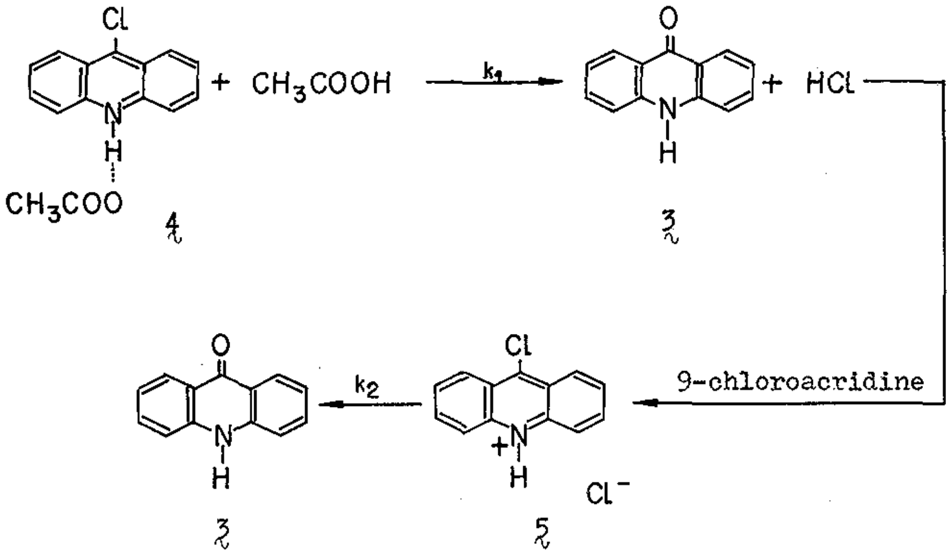
Figure 1. Absorption spectra of the reaction mixtures in solvolysis of 9-chloroacridine in 80 % acetic acid with 0.01 mm quartz cell. 1. 9-Chloroacridine, 1 m mole x dm^{-3}, 2. 9-acridanone.

Table 1

First-order rate constant and activation parameters for 9-chloroacridine hydrolysis in aqueous hydrochloric acid solution, concentration 1 m mole x dm^{-3}.

pH	K_I x 10^4 s^{-1}			$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
	40.0°C	60.0°C	70.0°C	KJ x mol^{-1}	J x mol^{-1} x deg^{-1}
0.0	0.154	1.06	2.66	83	-73
0.5	0.182	1.37	3.39	88	-56
1.0	0.218	1.74	4.25	85	-63
1.5	0.242	1.87	4.63	81	-76
2.0	0.269	2.18	4.97	84	-64
2.5	0.288	2.24	5.09	82	-70
3.0	0.295	2.41	5.20	83	-66

Figure 1 shows no traces of suggested π-complex **2** (well-formed isosbestic points at 366.2 and 409.3 nm). Then, aqueous hydrochloric acid was chosen as a reaction medium and surprisingly the hydrolysis rate constant in pH 1 at 70°C (K_I 0.000425 s^{-1}) turned out to be almost identical with the second-step rate constant found for the solvolysis of **1** at the same concentration in 80 % acetic acid (K_2 0.000433 s^{-1})[6]. As the pH value of 80 % acetic acid is also just equal to **1**, the conclusion is that 9-chloroacridine hydrochloride (**5**) is the true intermediate in the reaction under consideration and that the mechanism could be as follows:



9-Chloroacridine forms hydrogen bonded "acridinium acetate" (**4**) which reacts with another molecule of acetic acid affording **3** and, according to findings of Inoue et al.[9], acetyl chloride which hydrolyzes to give acetic acid and HCl. Then the hydrochloride **5** is formed which undergoes hydrolysis yielding **3**. Thus we observe a two-step consecutive kinetics of this reaction.

It seems possible that a hydrogen bonded compound **4** represents a common 9-chloroacridine "intermediate" reacting readily with various nucleophiles such as amines[3], carbanions[10], etc. to give rise to the corresponding 9-substituted acridines. This would explain an unusual catalytic action of such weak hydrogen donating acids as phenol and acetic acid. The importance of phenol in facilitating the reaction of **1** with a number of amines has been recognized by Magidson and Grigorovski[4] and since then it is widely used as a standard solvent for this condensation.[3] The addition of acetic or benzoic acid also improves both the rate and the yield in such condensations.[11] So, contrary to the widely accepted suggestion[12], it is not protonation but hydrogen bond formation at the nitrogen atom followed by the addition of nucleophile at position **9**, and the subsequent loss of the leaving group. Therefore, best results are usually obtained when **1** is condensed with a free amine (and not its hydrochloride)[3] but naturally in the presence of weak acids. Moreover, in the case of solvolysis of **1** in acetic acid, addition of a few molar equivalents of sodium acetate improves the reaction rate constant over twenty times as well as K_2/K_1 ratio from 0.05 in the absence to 0.5 in the presence of this agent for neutralizing chloride ions.[6] Moreover, the data given in Table 1 indicate that the lower pH (it means the more protonated 9-chloroacridine) the lower the reaction rate is observed.

In view of the above, it seems reasonable to consider the reaction as a solvolysis with 9-chloroacridine hydrochloride being intermediate.

EXPERIMENTAL

Materials: 9-Chloroacridine (**1**) was available from a previous study[13]. It was recrystallized twice, first from chloroform and finally from petroleum ether (40 - 60°C) to give crystals, mp 122°C (lit.,[14] 120°C). The buffers, HCl and NaOH were analytical grade commercial products and used without further purification. Acetic acid and benzene were freshly redistilled.

Kinetic Measurements: All kinetic measurements were monitored on a Beckman ACTA spectrophotometer equipped with a kinetic system between 320 and 500 nm. pH values were measured with a Radiometer (Copenhagen) pH meter. The reaction solutions for the hydrolysis in aqueous hydrochloric acid were prepared as follows: to 2.5 ml^3 of aq. HCl placed in a 1 cm quartz cell and thermostated in the spectrophotometer, ca. 0.1 mg of 9-chloroacridine was added and the contents magnetically stirred. 9-Chloroacridine easily dissolved and then absorption measurements were initiated. pH values were always checked before kinetic runs.

In a case of the solvolysis in 80 % acetic acid the following procedure was adopted: 10.65 mg (0.05 m mole) of 9-chloroacridine was dissolved in 0.5 ml of hot benzene and added to 50 ml of 80 % acetic acid heated to 70°C, then stirred vigorously for a minute or so and an aliquot of ca. 0.1 ml of the solution placed into a 0.01 mm quartz cell, this placed in a thermostated cell compartment and absorption measured. All the kinetic runs were done at least in duplicate.

ACKNOWLEDGEMENTS

This work was partly supported by grant 1074 from the Polish National Cancer Program. The author thanks Professor A. Ledóchowski for arousing his interest in this subject.

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Received, 2nd June, 1978