REACTIONS AT C^9 OF ACRIDINE DERIVATIVES. XV[1]. ON THE MECHANISM OF HYDROLYSIS OF 1-NITRO-9-AMINOACRIDINES[2]

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The hydrolysis rate constants for 1-nitro-9-aminoacridines are dissimilar to those for other 9-aminoacridines. These differences are discussed in terms of 9-iminoacridan ⇌ 9-aminoacridine tautomerism existing in aqueous solutions.

9-Aminoacridine derivatives have been attracting a good deal of attention for a long time primarily due to the recognition of their important biological activity. The carcinostatic action of several 9-aminoacridines has been also announced[3]. Studies on the structure-activity relationship have shown that the strongest anticancerous activity was exhibited by 1-nitro-9-aminoacridines[4] and 1-nitro-9-{3-dimethylaminopropylamino}-acridine dihydrochloride (C-283) after extensive investigations[5] has been registered as an antitumour drug.

Most physico-chemical properties of 1-nitro-9-aminoacridines differ essentially from those of nitro-group-free analogues. Much work has been done, among which kinetic investigations are of great importance[6]. Here we report a somewhat new interpretation of data published concerning the hydrolysis of 9-aminoacridine as well as of 1-nitro-9-aminoacridine derivatives[1,6,7].

The fundamental question in the kinetic investigations was why a nitro substituent should change the behaviour of 9-aminoacridines over the whole pH range[1].

Fig.1. indicates that 9-aminoacridines undergo hydrolysis much more easily in basic media whilst 1-nitro-9-aminoacridines react much more slowly under the same basic conditions[8].

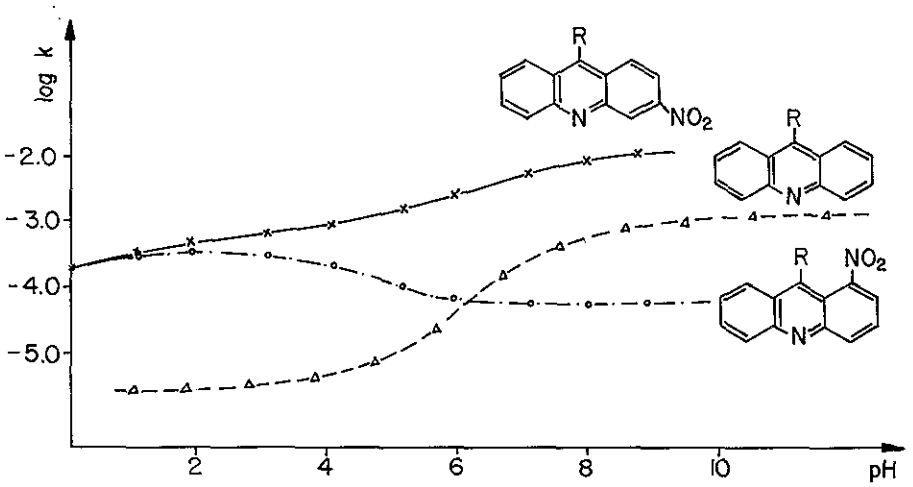
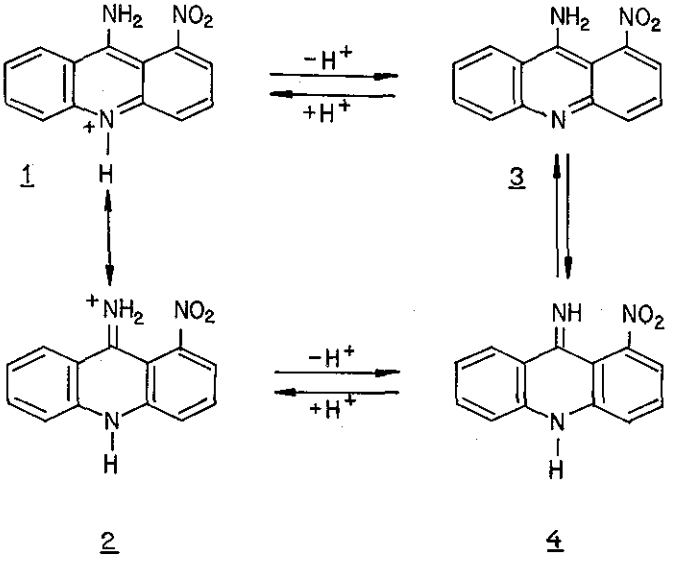


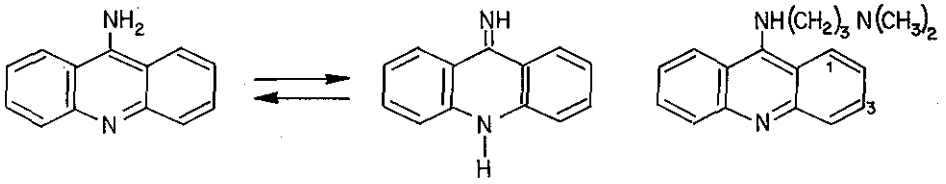
Fig.1. Plots of log k versus pH for C-137 (- - - - -), C-257 (———), and C-283 (—·—·—); R = $NH(CH_2)_3N(CH_3)_2$.

Particularly interesting conclusion can be drawn from a comparison of the hydrolysis rate constants of the two isomers with nitro group in positions 1 and 3 (C-283 and C-257, respectively). The observed trend of dependence of rate constants upon the pH is opposite, though the direction of both inductive and mesomeric effects is still the same in these compounds.

The observed phenomenon may be interpreted by assuming the existence of 1-nitro-9-aminoacridine in the following structures:



The 1-nitro-9-aminoacridinium cation can be written as for 9-aminoacridine[9] in the resonance forms 1 and 2. In weakly basic solutions, however, tautomeric equilibrium 3 ⇌ 4 must be considered. The question of whether 9-aminoacridine exists as the amino form 5 or as the imino tautomer 6 was controversial for a long time.



5 6 7

It is now accepted that 9-aminoacridine is an amino compound 5 and this conclusion is supported by various investigations[9]. But, when a strongly electron-withdrawing group is attached to the amino-nitrogen, as in 9-trichloroacetamidoacridine or 9-benzenesulfonamidoacridine, the compound adopts the imino form[10].

Dauter et al.[11] elucidated the crystal structure of 1-nitro-9-(3-dimethylaminopropylamino)-acridine mono hydrogen iodide salt and pointed out that this compound exists as the iminoacridan in the solid state. The iminoacridan structure also appears to exist in chloroform solution in the presence of europium (III), for the n.m.r. spectrum of their complex shows some shifts of signals corresponding to a hydrogen atom attached to the heterocyclic nitrogen[12].

Such a hypothesis is consistent with the kinetic data. The acridinium cation exists predominantly in the form of structure 1 and hydrolysis occurs with relative ease in acidic solution. But as the pH increases the acid-base equilibrium is shifted to the right structure 4 and the carbon-nitrogen bond which has double bond character inhibits nucleophilic attack at position 9 by water. Fig.1. shows that the reaction rate decreases as pH increases.

In contrast, the reaction rate increases for the 3-nitro derivative (C-257) as the pH rises, and the shape of the plot is similar to that for 9-aminoacridine. This is consistent with the supposition that the 9-amino tautomer is also strongly prefered for this 3-nitro compound.

For what reason do the above mentioned isomers differ from one another? If electronic effects are rejected then steric repulsion must be responsible. The usually unfavourable "imino-acridan"[13] form 4 is thus formed with less steric hindrance from the nitro group than in the amino structure 3. Alternatively, in the case of the 3-nitro isomer, in the absence of obvious steric interference, the compound must be assumed to be of aminoacridine type and to have a very strong tendency to remain that way. Two reasons for this can be advanced. The shape of a plot of log k versus pH for the compound C-257 resembles those of nitro-free analogues though this one is considerably shifted to the left[14]; therefore the 3-nitro group only decreases the electron density at the reaction site and makes nucleophilic substitution much easier over the whole pH range. The hydrolysis rate constants are similar under strongly acidic conditions indicating that the acridinium cations are of identical character (or nearly so).

Thus, we suggest that the steric demands of the substituents in the 1-nitro-9-aminoacridine derivatives are competing with the electronic requirements of aromaticity preventing the full adoption of one or other of the alternative (3 or 4) structures. We can therefore observe a typical example of compensation effect over the large range of the pH.

References and Notes

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14. Detailed kinetic data including those for the 2-nitro and 4-nitro isomers of 7 will be published elsewhere. Preliminary results show no difference in quality between the 2-, 3-, and 4-nitro isomers. This supports our hypothesis.

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