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KINETICS OF THE ACID AND ALKALINE DEGRADATION OF OXYTETRACYCLINE HYDROCHLORIDE

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ABSTRACT

The kinetics of the acid degradation of oxytetracycline hydrochloride in absence and in presence of Fe(III) and/or Cu was followed spectrophotometrically at 245 nm. The reaction was found to be first order in oxytetracycline, in hydrogen ions and is inhibited by the presence of cations. Values of 96 and 54 kJ mol^{-1} were obtained for the overall energy of activation, and the corresponding values for the entropy of activation are -4.2 and -117 JK^{-1}. The products of the reaction were identified by TLC as α- and β-apoterramycin.

The alkaline degradation was traced at 380 nm. The reaction followed first order kinetics in both reactants and was unaffected by the presence of cations. Values of 65 kJ^{-1} mol^{-1} and -96 JK^{-1} were obtained for the activation parameters.

INTRODUCTION

Oxytetracycline hydrochloride is the most important among the broad spectrum antibiotics. Pasternack et al (1) and Hochstein et al (2) pointed out that the dehydration of ring "C" in oxytetracycline, scheme I, is the first change to occur when the antibiotic was treated with dilute acids to give the inactive anhydroterramycin, II, which rearranges rapidly to form apoterramycin, III, which exists in two mutually interconvertible forms with identical U.V. spectra.

As for the alkaline degradation of oxytetracycline, terracinoic acid, IV, was identified as the main product which results from the fundamental rearrangement in the molecule following the scission of C-C bonds in "B" and "C" rings of the antibiotic (1,3,4).

The present study deals with the kinetics of degradation of oxytetracycline hydrochloride in acid and in alkaline media together with the effect of cations such as iron (III) and copper (II) on the reaction rate.

EXPERIMENTAL

Oxytetracycline hydrochloride was kindly supplied by CID Company for pharmaceuticals, as 99%. All other chemicals were of reagent grade. α- and β-apoterramycin were prepared according to the procedure reported by Hochstein et al (2) and was used as reference spots in the identification of the product

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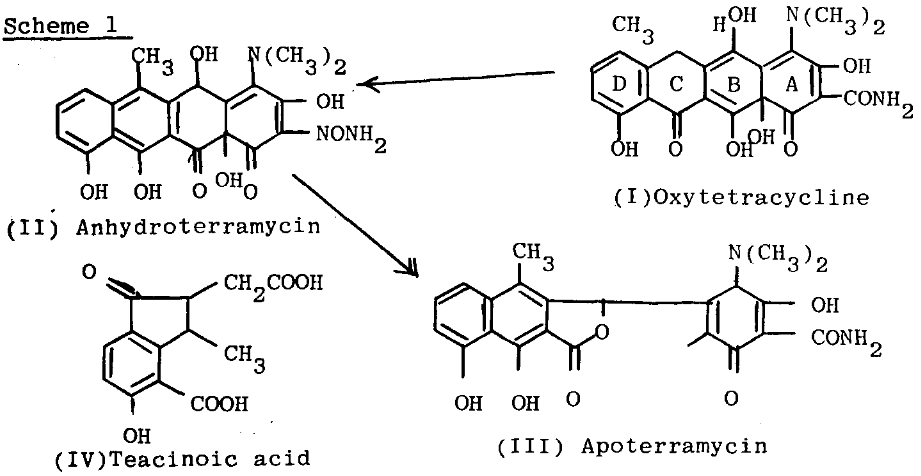
Scheme 1



of the acid hydrolysis by TLC (7).

The reaction was followed on a Unicam SP 8000 Spectrophotometer.

The acid and the alkaline hydrolysis of oxytetracycline alone or in the presence of ferric chloride in the ratio 3:1* and/or copper sulphate in the ratio 2:1* was followed spectrophotometrically at 245 nm and 380 nm for the acid and the alkaline hydrolysis, respectively. The effect of the concentration of oxytetracycline hydrochloride, hydrochloric acid or potassium hydroxide and temperature on the reaction rate was studied. The effect of each factor was investigated whilst keeping all the other variables fixed.

The product of the reaction was identified by TLC using CC_{41} cellulose plates, supplied by Whatmann, and α- and β-apoterramycin as reference solutions (5) and the precipitate thus obtained was microanalyzed.

RESULTS AND DISCUSSION

Acid Hydrolysis of Oxytetracycline Hydrochloride

TLC showed that the reaction went to completion and that α and β-apoterramycin were the only products of the reaction (3,7,8).

The reaction was found to be first order and some of the pseudo first order plots are shown in Fig. 1. The values of the observed first order rate constant at various conditions were evaluated from the slopes of such lines.

The reaction is inhibited by the cations, Table 1, attributed to the stabilization of oxytetracycline hydrochloride by chelation, Kaplan et al reported the inactivation of the acid degradation of oxytetracycline with cupric-morpholine complex (9).

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*The reported ratios for the complexes formed (6).

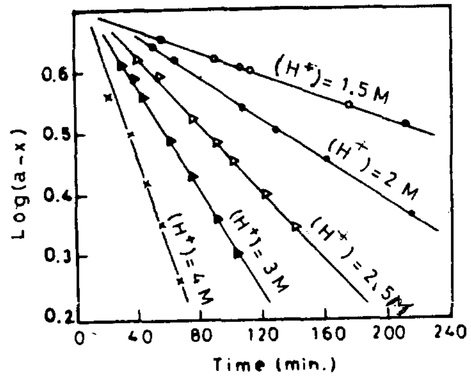

Fig.1 First order plots for the acid hydrolysis of oxytetracycline hydrochloride at 31°C [antibiotic]= 1.25 x 10^{-5}M.

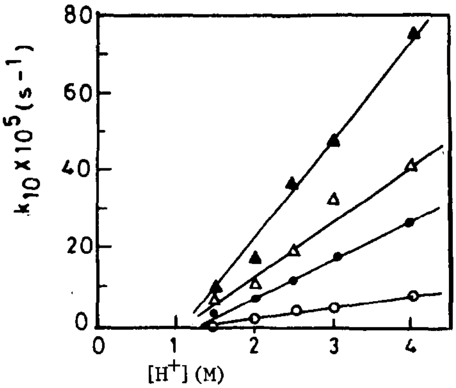

Fig.2 Variation of k_{10} with hydrogen ion concentration, [antibiotic] = 1.25 x 10^{-5}M.

Hydrochloric acid accelerated the hydrolysis of tetracycline hydrochloride and a linear relationship was obtained between k_{10} and hydrogen ion concentration which intersects the abscissa at ca 1.2 M, Fig. 2, indicating that the antibiotic resists degradation below this acidity and thus it is safe to administer it orally. Waller et al (10) and Stephens et al (11) pointed out that oxytetracycline hydrochloride is chemically stable in solutions of acidity 0.03 M.

Alkaline Hydrolysis of Oxytetracycline Hydrochloride

TLC gave three spots, two are unstable and the third one last for almost two days and was identified as terracinoic acid,IV. It was reported earlier that the degradation of the antibiotic in alkaline medium yielded ammonia and dimethylamine and that the major product was terracinoic acid (4,5). The reaction was found to be first order in the antibiotic and to be unaffected by the cations. The values of the observed first order rate constant bear a linear relationship with hydroxyl ion concentration.

Applying Arrhenius equation and the theory of absolute reaction rates, values of the energy of activation, Ea, and the entropy of activation, ΔS^*, were evaluated and given in Table I, which shows that the entropy of activation for the acid catalyzed reaction plays a prime role in the reaction rate.

The negative values obtained for the entropy of activation, are indicative of the involvement of ionic reactions in the transition state and are determined mainly by the loss of translational and rotational degrees of freedom as several particles come together to form the activated complex and according to Rosotti (13) a change of entropy of ca-105 JK^{-1} is expected for such transformation.

Table 1. Kinetic and thermodynamic parameters for the hydrolysis of oxytetracycline hydrochloride.

Reaction medium	$k_o (s^{-1})$, 22°C	$E_a (kJ\ mol^{-1})$	$\Delta S^* (JK^{-1}\ mol^{-1})$
Acidic	5.0×10^{-5}	96	-4.2
Acidic in presence of cations	3.8×10^{-5}	94	-117
Alkaline	3.0×10^{-4}	65	- 96

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