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KINETICS OF HYDROLYSIS OF XYLOMETAZOLINE (XYL) IN AQUEOUS SOLUTION

Beate Stanisz

Department of Pharmaceutical Chemistry, University of Medical Sciences, Poznań, Poland

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Abstract

The effect of pH (over the range of 2.10 - 11.90) and temperature (from 353 to 363 K) on the stability of xylometazoline (XYL) has been studied by high performance liquid chromatography (HPLC). Using the dependence of $\log k$ vs pH, the hydrolysis of both the undissociated and dissociated XYL-molecules has been described by micro rate constants k_1 and k_2 . Thermodynamic parameters (activation energy, enthalpy and entropy) of the composition reaction were calculated.

Keywords: Xylometazoline hydrochloride (XYL), stability in aqueous solution, first-order rate constants

INTRODUCTION

Xylometazoline hydrochloride 2-(4,1,1-dimethylethyl-2,6-dimethylbenzyl)-2-imidazoline hydrochloride belongs to the group of nonselective adrenergic drugs. XYL is used in topical application to relieve nasal congestion associated with acute or chronic rhinitis, common cold, sinusitis and hay fever or other allergies [1-6]. The available literature lacks data pertaining to the stability of XYL in aqueous solution, although the products of decomposition have already been isolated and identified [7].

The aim of this study was to investigate the stability of XYL as a function of concentration of the respective buffer species and temperature to determine the catalytic rate constants for the hydrolysis of XYL as well as to formulate the respective kinetic equations.

EXPERIMENTAL

Materials and reagents

Xylometazoline hydrochloride (Sigma-Aldrich Co.), Nipagine A (internal standard) (Sigma-Aldrich Co.). The above-mentioned, as well as all other chemicals used in this study were of analytical grade.

Analytical procedure

The analytical system included a pump (Shimadzu), UV-detector, a Rheodyne 20 μ L syringe loading injector and RP-18 (250 mm x 4 mm, 10 μ m particle size) (Merck). The flow rate of the mobile phase was 1.0 mL/min and the eluent was monitored at 220 nm. A mixture of methanol – water – triethylamine (40:58:2 v/v) was used as the mobile phase throughout the kinetic investigations.

The initial concentration of XYL was 2.8×10^{-4} mol/L. Nipagine A at a concentration of (0.16 mg/L) was used as the internal standard.

Validation method

Linearity of HPLC: the ratios of the chromatographic peak heights and the concentrations of XYL for range from 0.02 mg/mL to 0.10 mg/mL were used to assess this parameter.

Selectivity: the developed method is selective with respect to the degradation products and internal standard (Nipagine A).

Precision: of measurements of XYL decomposition were validated on the basis of 8 independent determinations carried out under identical experimental conditions, and determination of the rate constants of XYL decomposition in 0.5 mol/L aqueous NaOH at 363 K. The results show that the adopted procedure for determination of XYL is characterized by an appropriate RSD (1.09%).

Kinetic measurements

The kinetic studies of the reaction of hydrolysis of XYL included the following procedures:

- estimation of apparent rate constants of hydrolysis over the pH range of 2.10 -11.90 at three experimentally chosen temperatures: 353, 358 and 363 K;

- estimation of effects exerted by the concentration and type of buffers used in the experiment on the rate of hydrolysis (general acid-base catalysis);
- estimation of k_{pH} values, pertaining to the specific acid-base catalysis,
- determination of the $\log k_{pH} = f(pH)$ relationship by means of a suitable kinetic equation;
- estimation of catalytic rate constants of partial reactions;
- estimation of thermodynamic parameters of partial reactions.
- To obtain the desired pH of the solutions, the following buffers were used: phosphate buffers (H_3PO_4/KH_2PO_4 – pH range 2.10 to 3.10 and KH_2PO_4/Na_2HPO_4 - pH range 5.90 to 7.20); acetate buffer (CH_3COOH/CH_3COONa , (pH range 3.50 to 5.70); borate buffer ($NaOH/H_3BO_3$ - pH range 8.20 to 10.40); NaOH solution pH range 11.30 to 11.90)

The composition of respective buffers were calculated on the basis of the Henderson-Hasselbalch equation [8]. The ionic strength (μ) of all solutions was adjusted to 0.5 mol/L with a solution of sodium chloride (4 mol/L). 2 mL aliquots of the solution were transferred into 5 mL ampoules and sealed.

The concentrations of XYL were established for each sample under investigation, and values obtained at t_0 – were taken as c_0 . The remaining ampoules were immediately heated to 353, 363 or 368 K, respectively. After experimentally determined time intervals – the samples were cooled to room temperature and neutralized to pH 7.0. Next, 1.0 mL of the solution obtained was mixed with 1.0 mL of internal standard solution and subjected to analysis.

The pH for NaOH solutions was calculated from an equation derived from the literature [8]. The pH of other samples was measured by means of a potentiometric pH-meter (n 517 Mera Elwro, Wrocław, Poland) at the respective experimental temperatures (353, 363 and 368 K).

RESULTS AND DISCUSSION

Estimated rate constants of hydrolysis

The estimated first-order rate constants of XYL hydrolysis were determined by HPLC using the following equation:

$$\ln(h_i/h_{in}) = \ln(h_o/h_{in}) - k_{est} \cdot t$$

where: k_{est} stands for the experimentally obtained rate constants. The estimated rate constants were equal to the slope of $\ln(h_i/h_{in})$ vs $f(t)$ plots.

In samples containing phosphate buffer (pH range 2.10 to 3.10), borate buffer (pH range 8.20 to 10.40) and sodium hydroxide, k_{est} was equal to the k_{pH} .

For samples containing acetate and phosphate (pH range 5.90 - 7.20) buffers, the respective estimated rate constants were calculated as follows:

$$k_{\text{est}} = k_{\text{pH}} + k_{\text{B}}[\text{B}]_{\text{T}}$$

where: $[\text{B}]_{\text{T}}$ represents the total buffer concentration, k_{B} - the catalytic effect of the respective buffer (Fig. 1).

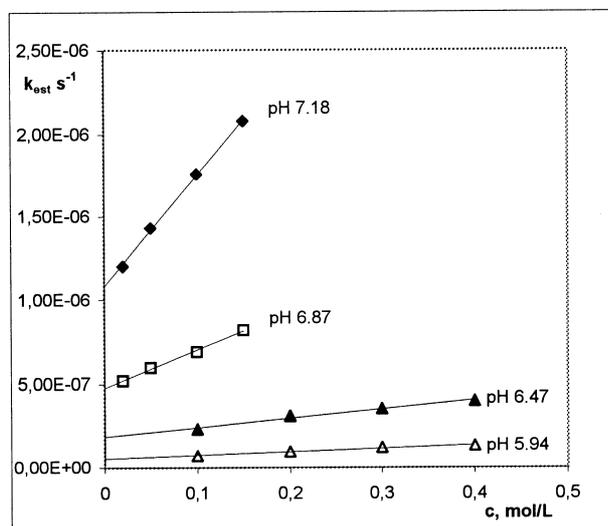


Fig. 1. Plots of the pseudo-first-order rate constant vs total phosphate buffer concentration for degradation of XYL at various pH values and 353 K

Log k_{pH} vs pH profile

The semilogarithmic relationship k_{pH} vs $f(\text{pH})$ indicates that the specific acid-base catalysis of the XYL decomposition is in fact a spontaneous hydrolysis caused by water and is dependent on the charge of the substrate (Fig. 2).

Over a pH range from 2.10-11.90, there exist two different ionic forms of this compound, and these forms are in equilibrium. This means that the value of k_{pH} is the sum of two individual partial reactions.

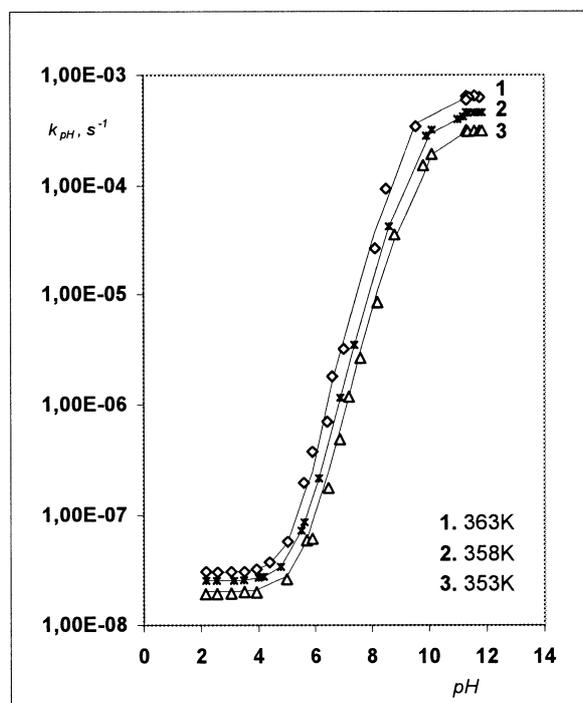
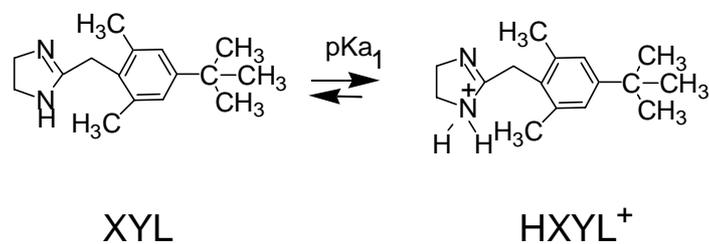


Fig. 2. Log k_{pH} for the hydrolysis of XYL in aqueous solution at several temperatures

The hydrolysis of the imidazolyl group of XYL may be described by the following equation: $k_{pH} = k_1 f_{HXYL^+} + k_2 f_{XYL}$

where k_1 and k_2 are first-order rate constants for the water-catalyzed degradation of different ionic forms of XYL; and f_{XYL^+} and f_{XYL} represent the molar fractions of undissociated and dissociated forms of XYL.

pK_a values of XYL hydrochloride were derived from the profile: $\log k$ vs $f(\text{pH})$ and are equal to 9.40 at 363 K, 9.50 at 358 K and 9.60 at 353 K.

Table 1

Catalytic rate constants and thermodynamic parameters for hydrolysis of XYL in aqueous solutions

Reaction $\text{HXYL}^+ + \text{H}_2\text{O} \rightarrow \text{products}$, k_1			
Temperatures (K)	$(k_1 \pm \Delta k_1) \times 10^8 \text{ s}^{-1}$	Statistical evaluation $\ln k_1 = f(1/T)$	Thermodynamic parameters
363	1.94 ± 0.68	$a = -7764.14 \pm 313$	$E_a = 64.5 \pm 2.6$ [kJ/mol]
358	2.61 ± 0.99	$b = 4.22 \pm 0.87$	$\Delta H^\ddagger = 62.1 \pm 2.6$ [kJ/mol]
353	3.50 ± 0.58	$r = -0.999$	$\Delta S^\ddagger = -209.8 \pm 7.2$ [J/(K·mol)] $\ln A = 4.22$
Reaction $\text{XYL} + \text{H}_2\text{O} \rightarrow \text{products}$, k_2			
Temperatures (K)	$(k_1 \pm \Delta k_1) \times 10^8 \text{ s}^{-1}$	Statistical evaluation $\ln k_2 = f(1/T)$	Thermodynamic parameters
363	4.49 ± 0.92	$a = -4053.60 \pm 285$	$E_a = 33.7 \pm 2.3$ [kJ/mol]
358	5.23 ± 0.69	$b = 3.76 \pm 0.79$	$\Delta H^\ddagger = 31.2 \pm 2.3$ [kJ/mol]
353	6.11 ± 0.78	$r = -0.999$	$\Delta S^\ddagger = -213.6 \pm 6.7$ [J/(K·mol)] $\ln A = 3.76$

Catalytic rate constants (Table 1)

The catalytic rate constants k_1 were determined using the value of k_{pH} at pHs ranging from 2.10 to 4.50 (where $f_{\text{XYL}^+} \rightarrow 0$). They were equal to the arithmetic

mean from five k_{pH} values within this pH range. The catalytic rate constants k_2 were determined using the value of k_{pH} over pHs from 11.30 to 11.90 (where $f_{\text{XYL}} \rightarrow 0$). They were equal to the arithmetic mean from five k_{pH} values in this pH range.

Thermodynamic parameters (Table 1)

Activation energies as well as enthalpies and entropies values for the degradation of XYL at 298 K were calculated. The established negative entropy suggests a double molecular model of reaction with participation of water molecules.

CONCLUSIONS

- The degradation of XYL is the result of spontaneous hydrolysis of XYL molecules caused by water.
- The hydrolysis of XYL is catalyzed by sodium acetate (CH_3COONa) and hydrophosphate ions (HPO_4^{2-}).
- Hydrolysis of XYL was found to occur at minimal rates over a range of pH from 2.00 to 4.00.
- With known values of rate constants and activation energies of the reactions involved, it is possible to calculate rate constants of the acid-base catalyzed hydrolysis of XYL at various temperatures and different pH's. However, the function: $\ln k_i$ vs $f(1/T)$ must be a straight line relationship.

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