

Titrimetric micro determination of hydroxyzine using Oxone

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Research Article

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Abstract

The kinetics of the oxidation reaction of hydroxyzine hydrochloride with potassium hydrogen peroxomonosulfate was studied depending on the pH of the medium. It was established for the first time that the kinetics of the reaction of N-oxidation of hydroxyzine obeyed the general laws of the mechanism of specific acid-base catalysis, proceeded quantitatively and stoichiometrically according to the mechanism of nucleophilic substitution of the β -oxygen atom of the peroxyacid group of peroxomonosulfate ions. It was shown that quantitative oxidation was achieved in 1–1.5 minutes at pH 8.0–8.5. The only reaction product was hydroxyzine N-oxide. A scheme of the oxidation process was proposed. Techniques were developed and the possibility of quantitative determination of hydroxyzine hydrochloride in the substance and tablets of 25 mg by iodometry using Oxone as an analytical reagent was shown. A known excess of reagent was added, and after a predetermined time, the residual reagent was determined iodometrically. $RSD \leq 1.52\%$. $(\bar{x} - \mu) \cdot 100 / \mu < RSD$. The procedures had several advantages such as speed, simplicity, accuracy, selectivity, and cost-effectiveness, and therefore could be easily adapted by quality control laboratories for routine analysis.

Introduction

Hydroxyzine dihydrochloride (HDH) [2192-20-3], chemically known as (RS)-2-{2-[4-(p-chlorophenylbenzyl)piperazin-1-yl]ethoxy}ethanol dihydrochloride (Fig. 1), is the first-generation antihistamine of the piperazine class that is an H1 receptor antagonist, that exhibits sedative, anxiolytic, and antiemetic properties [1, 2].

Drug substance Hydroxyzine Hydrochloride is monographed in the PH (Ph Eur. [3], BP 2020 [4], USP 2019 [5]). The pharmacopoeia method is based on the potentiometric titration of HDH in non-aqueous medium using perchloric acid [4]. The official USP method which is also available for the assay of the drug in tablets employs a chromatographic system equipped with a UV-detection, where HDH can be detected at 232 nm [5].

Determination of HDH in pharmaceutical preparations is important for pharmaceutical needs, and hence it is crucial to develop simple, sensitive, selective, and cost-effective methods for its determination as apart of compliance of specifications study: specimen quantity, sample homogeneity, and content uniformity in tablets.

Different methods have been used for the determination of the antihistaminic drug HDH including HPLC [6], GC [7], spectrophotometry [8], potentiometry [9], voltammetry [10], capillary zone electrophoresis using chiral selectors [11] and titrimetry [12]. So, a titrimetric assay of some antihistamines through the determination of the chloride of their hydrochlorides has been reported. The chloride content of the drug is determined by titration with mercury (II) using diphenylcarbazone-BTB as indicator [12]. Two simple titrimetric methods have been developed for the determination of hydroxyzine dihydrochloride (HDH) in pure form and in tablets. The principle of the methods are simple acid-base reactions in which the

hydrochloride content of the drug was determined by titrating with an aqueous standardized NaOH solution either visually using phenolphthalein as indicator (method A) or potentiometrically (method B) using glass-calomel electrode system. The methods were applicable over the range of 2–20 mg HDH.

The procedures were also applied for the determination of HDH in its dosage forms and the results were found in good agreement with those obtained by the reference method [13]. Two simple, rapid, reliable, precise and accurate and cost-effective non-aqueous titrimetric procedures have been developed for the determination of hydroxyzine dihydrochloride (HDH) in bulk drug and its pharmaceutical formulations. The methods are based on the titration of the drug in glacial acetic acid in the presence of mercuric acetate with acetous perchloric acid to the visual end point using crystal violet as indicator [14].

An inspection of most of the available methods for the above-mentioned drug reveals that most of them are either cumbersome or time consuming, or involve the use of expensive equipment and reagents. On the other hand, titrimetry is the simplest analytical techniques extensively used in the drug standardization laboratories.

Redox titrimetry may serve as useful alternative to many of the aforesaid sophisticated techniques because of their cost effectiveness, ease of operation, sensitivity, remarkable accuracy and precision, and wide applicability.

The present investigation aims to develop simple, sensitive, and cost-effective method for the determination of HDH in pure form and tablets using redox titrimetric technique. The method involves the use of potassium hydrogenperoxomonosulphate (KHSO₅, PMS) in form Oxone (the triple salt 2KHSO₅·KHSO₄·K₂SO₄) as the titrant.

Experimental

Materials

Chemicals

Hydroxyzine hydrochloride - Sigma-Aldrich, Synonym: Hydroxyzine dihydrochloride. Empirical Formula: C₂₁H₂₇ClN₂O₂·2HCl. CAS Number:2192-20-3; Molecular Weight: 447.83 g/mol; Certificate data: 99.6% (purity by perchloric acid titration according to document N^o H8885/05/07/08/1).

ATARAX® film-coated tablets 25 mg, No. 25 tablets in a blister, Series of medicinal product No. 313517. Manufacturer USB Pharma S.A., Belgium

Analysis certificate: 98.5%, series number: 313517. *Excipients*: microcrystalline cellulose (Avicel PH102®), colloidal silicon anhydride (Aerosil 200®), magnesium stearate, lactose monohydrate, Opadry® Y-1-7000 (titanium dioxide, hydroxypropyl methylcellulose 2910, macrogol 400).

OXONE®, monopersulfate compound - Sigma-Aldrich; CAS Number: 70693-62-8 ; Molecular Weight: 307.38 g/mol; % Active oxygen (A.O.) = 4.5 (titration by $\text{Na}_2\text{S}_2\text{O}_3$). A stable 2:1:1 ternary compound of this salt, potassium hydrogen sulfate, and potassium sulfate that is available under the trade names Oxone and Caroate is frequently employed as a source of the peroxymonosulfate.

Solution of potassium hydrogen peroxomonosulfate (KHSO_5), 0.04 mol/l. About 1.4 g of KHSO_5 powder was dissolved in 70 ml of double-distilled water in a 100 ml volumetric flask, made up to the mark with water and mixed thoroughly. The exact concentration was determined by iodometric titration.

For this 10 ml of the solution was taken with a pipette and transferred into a 100 ml volumetric flask. The volume was brought to the mark with double-distilled distilled water. Then 10.00 ml of the resulting solution was taken and transferred to a 100 ml conical Erlenmeyer flask, 1 ml of a $0.01 \text{ mol l}^{-1} \text{ H}_2\text{SO}_4$ solution was added and, with vigorous stirring, 2 ml of a 5% KI solution. The released free iodine was immediately titrated with 0.01 mol/l sodium thiosulfate solution. Based on the results of three repeated experiments, the molar concentration of KHSO_5 was calculated using the formula:

$$c(\text{KHSO}_5) = V(\text{Na}_2\text{S}_2\text{O}_3) \times 0.0100 \times 100.00 / 10.00 \times 10.00 \times 2.$$

Solutions of $c(\text{Na}_2\text{S}_2\text{O}_3, f = 1) = 0.1 \text{ mol/l}$ of sodium thiosulfate and $c(\text{H}_2\text{SO}_4) = 1 \text{ mol/l}$ of sulfuric acid were prepared from fixanals of the standard titer. A 0.02 mol/l sodium thiosulfate solution was used as a titrant, which was prepared by the appropriate dilution of the original solution with distilled water. To measure the titrant volume with an accuracy of $\pm 0.01 \text{ ml}$, a 10 ml class 2 microburette was used. A 5% solution of potassium iodide was produced by the volume-weight method.

Preparation of 0.2 mol L^{-1} Phosphate buffer solution (pH 8.3) 35.75 g Crystallized disodium hydrogen phosphate dodecahydrate ($\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$) was dissolved in 500 mL flask using double-distilled water. 19 mL of 0.1 M solution of Hydrochloric acid solution was added. pH of the final solution was controlled potentiometrically.

Sodium Phosphate dibasic, $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ (puriss.), CAS – 7558-79-4, produced by «ReaChem», Kharkiv, Ukraine.

Sodium hydroxide solutions were prepared by diluting a previously obtained concentrated (50% w/w) solution with distilled water.

Other chemicals and reagents such as hydrochloric acid and potassium iodide used were of analytical grade from Qualigens. All reagents and solutions were prepared using this distilled water.

The pH value of the solutions was controlled using a glass electrode ESL-43-07 on an ionometer "Ionomer laboratory I-160M" (Belarus) paired with an argentum chloride electrode EVL-1M3.1 saturated with potassium chloride.

The reaction product was identified by reacting desired quantity of the hydroxyzine with potassium hydrogen peroxomonosulphate in sodium bicarbonate solution and keeping the reaction mixture for one hour for completion of the reaction. One of the products was extracted with ether, the organic layer obtained was separated and treated with distilled water. The ether layer was evaporated and dried to get product. The product obtained is Hydroxyzine *N*-oxide (melting point 170–172°C (dec.)). It is confirmed by IR- and ¹H NMR -spectroscopy.

Infrared Spectrum of isolated Hydroxyzine oxidation product. Principal peaks at wavenumbers, cm⁻¹ (KBr disk): 2825, 1685.5, 1591, 1488, 1454, 1367, 1127, 939 (N⁺-O⁻), 804, 761, 721, 703, 665.

The ¹H NMR spectrum of isolated Hydroxyzine oxidation product was compared to NMR of Hydroxyzine [15]. The number of protons in the aromatic region of the ¹H NMR of the degradation product was similar to that of Hydroxyzine, indicating formation of *N*-oxide. The *N*-oxide effect can be observed by the difference in the chemical shifts of the proximal protons adjacent to the *N*-oxide carbons (Fig. 2). The deshielding influence of the *N*-oxide function, generated on the nitrogen bearing the ethoxyethanol chain, causes a down-field shift of the piperazine ($\Delta\delta = 0.2$) and ethoxy ($\Delta\delta = 0.5$) protons.

The melting point was determined by the open capillary method on a PTP-M instrument (instrument for determining the melting point of solids).

Method for registration of IR spectra. IR spectra were recorded at 650–4000 cm⁻¹ on a SPECORD M-80 spectrometer manufactured by Zeiss, Jena, Germany. Tablets were prepared by mixing 200 mg of potassium bromide and 2 mg of the test compound (1% concentration) followed by compression in the standard manner.

The NMR measurements were carried out on a 400 MHz Varian spectrometer. The NMR spectra were measured in D₂O.

Results And Discussion

Study of the kinetics of the N-oxidation of hydroxyzine with potassium hydrogen peroxomonosulphate in aqueous medium.

The results of studying the kinetics of the reaction of *N*-oxidation of Hydroxyzine with potassium hydrogen peroxomonosulfate by the method of iodometric titration (according to the consumption of the oxidizing agent) depending on the pH are shown in Fig. 3.

$$\alpha(\text{Hyd}) = 1.35 \cdot 10^{-3} \text{ mol l}^{-1}; \alpha(\text{KHSO}_5) = 2.05 \cdot 10^{-3} \text{ mol l}^{-1}$$

The dependence of the observed second-order constant of the reaction of *N*-oxidation of Hydroxyzine with potassium hydrogenperoxomonosulfate on the pH of the medium is shown in Fig. 4.

As can be seen, the maximum rate of the reaction of *N*-oxidation of hydroxyzine with potassium hydrogen peroxomonosulfate is reached at pH 8.3. It can be assumed that the non-protonated form of the base of the tertiary Nitrogen Hydroxyzine (Hyd₀) and the hydrogenperoxymonosulfate monoanion (HSO₅⁻) take part in the reaction. Based on this assumption, we derived the kinetic equation for the reaction:

$$\text{Rate} = k_{\text{obs}} \cdot \alpha(\text{Hyd}_0) \cdot \alpha(\text{KHSO}_5)$$

$$k_{\text{obs}} = k \alpha(\text{Hyd}_0) \cdot \alpha(\text{HSO}_5^-)$$

where, $\alpha(\text{Hyd}_0)$ is the mole fraction of the Hydroxyzine base;

$\alpha(\text{HSO}_5^-)$ is the molar fraction of hydrogen peroxymonosulfate monoanion;

which are respectively equal to:

$$\alpha(\text{Hyd}^0) = K_a / (K_a + [\text{H}^+]) = \alpha(L\text{-Hyd}^0) = 10^{-7,4} / (10^{-7,4} + 10^{-\text{pH}});$$

$$\alpha(\text{HSO}_5^-) = (10^{-0,4} \cdot 10^{-\text{pH}}) / [(10^{-\text{pH}})^2 + (10^{-0,4} \cdot 10^{-\text{pH}}) + (10^{-0,4} \cdot 10^{-9,4})];$$

K_a is the dissociation constant of the acid form of Hydroxyzine;

It should be taken into account that $\text{pH} = -\lg [\text{H}^+]$, and $[\text{H}^+] = 10^{-\text{pH}}$.

$\text{p}K_a = -\log K_a$, and $K_a = 10^{-\text{p}K_a}$. $\text{p}K_a \text{ Hyd} = 7.4$.

The Caro acid has two dissociation constants, which are expressed as the following $\text{p}K_a$ indicators, respectively: $\text{p}K_{a1} = 0.4$ and $\text{p}K_{a2} = 9.4$.

The linear dependence with k_{obs} on the production of molar fractions of the Hydroxyzine base and the HSO₅⁻ monoanion (Fig. 5) indicates the correct assumption that it is the Hydroxyzine base and mainly the hydrogen peroxomonosulfate acid monoanion that take part in the reaction (correlation coefficient $R = 0.9$, which is close to 1).

The scheme of the process of oxidation of Hydroxyzine potassium hydrogen peroxomonosulfate is shown in Fig. 6.

Thus, it has been established that the reaction kinetics obeys the general laws of specific acid-base catalysis. The stoichiometric ratios and interaction time in the reaction were established: 1 mol of KHSO₅ is consumed per mol of Hydroxyzine hydrochloride; stoichiometric consumption of the oxidizing agent at pH 8-8.5 is achieved in 1-1.5 minutes.

The obtained results of studying the reaction kinetics were used by us as the basis for the development of a new method for the quantitative determination of Hydroxyzine by the *N*-oxidation reaction using potassium hydrogen peroxomonosulfate as an analytical reagent.

Method for the quantitative determination of Hydroxyzine hydrochloride (HDH) in model (reference)

solutions. An aliquot of 1.00–10.00 mL of a solution containing 2.5–25 mg of HDH was placed with a pipette into a 100 mL Erlenmeyer flask; after that, 1 ml of NaOH (0.02 M), 5.0 ml of 0.2 M buffer solution (pH 8.3), 5.00 ml of KHSO₅ (0.008 M) were successively added and left for a certain time (1 min) at room temperature to complete the oxidation of the drug. To lower the pH, 1.0 ml of 1.0 M H₂SO₄ solution and then 2 ml of 5% potassium iodide were added while stirring the contents of the flask. The mixture was again left for about 10 seconds, and the liberated iodine was titrated with 0.01 M thiosulfate, while 1 ml of 1% starch solution was added near the end point. The whole procedure was also applied in a blank determination on water.

Method for quantitative determination of the content of the main substance in the substance Hydroxyzine dihydrochloride.

An accurate weight of 0.22392 g of the powder of the HDH substance with a known content of the main substance was dissolved in 70 ml of double-distilled water in a 100 ml volumetric flask, diluted with water to the mark and mixed well. A 20.00 ml aliquot of the drug solution was transferred into a 100 ml volumetric flask, 60 ml of pH 8.3 buffer solution and 5.00 ml of KHSO₅ (0.04 M) were successively added, the volume was finally diluted with water to 100 ml and mixed well. After 1 min, an aliquot of the reaction mixture (10.00 ml) was quickly added to the Englemeyer flask, which already contained 1 ml of 1 M H₂SO₄ solution, and immediately after that, 1 ml of 5% potassium iodide solution was added with shaking. The mixture was again left for about 5–10 seconds and the released iodine was titrated with 0.01 M thiosulfate with the addition of 1 ml of 1% starch solution near the end point. Similarly, a blank determination was performed with water instead of a solution of the analysed substance.

The content of the main substance in the substance of Hydroxyzine dihydrochloride in terms of dry matter (*w*, %) was found by the formula:

$$w = \frac{(V_0 - V) \cdot T \cdot 100 \cdot 100 \cdot 100\% \cdot 100\%}{10 \cdot 20 \cdot a (100 - w (H_2O))},$$

where V_0 is the volume of standard 0.0100 mol/l sodium thiosulfate used for titration in the control experiment, ml;

V is the volume of standard 0.0100 mol/l sodium thiosulfate used for titration in the working experiment, ml;

100 and 100 is volumes of volumetric flasks, ml;

20 is taken for the analysis of the volume of the solution of the dosage form, ml;

a is the mass of the sample of the substance, g

w(H₂O) is moisture content in the substance (mass loss upon drying),%;

10 is the volume of the reaction mixture taken for titration, ml.

T is the amount of Hydroxyzine dihydrochloride (C₂₁H₂₉Cl₃N₂O₂), which corresponds to 1 ml of a standard 0.0100 mol/l thiosulfate solution, g/ml;

1.00 ml of standard 0.0100 mol/l sodium thiosulfate corresponds to 0.00223915 g ml⁻¹ of hydroxyzine dihydrochloride (C₂₁H₂₉Cl₃N₂O₂), which should be 99–101% in the preparation in terms of anhydrous substance

Method for the quantitative determination of Hydroxyzine hydrochloride in tablets of 0.25 g

Twenty tablets were accurately weighed and ground into a fine powder. An accurately weighed amount of ground powder, equivalent to 250 mg of Hydroxyzine hydrochloride, was transferred into a 100 ml volumetric flask. 60 ml of water was added and the contents were thoroughly shaken for 15–20 minutes to extract the drug into the liquid phase, the volume was finally adjusted to the mark with water, mixed well and filtered using Whatman No. 42 filter paper. An aliquot of the filtrate (25 mg/ml) was used for the method described above (see "*Method for the determination of Hydroxyzine dihydrochloride in model (reference) solutions*").

The results of the titrimetric determination of Hydroxyzine dihydrochloride in model solutions using Oxone are given in table.1. For hydroxyzine dihydrochloride levels of 2.24 mg and 22.40 mg, the relative standard deviation is 2.5% and 0.43%, respectively. $\delta < \text{RSD}$.

Table 1
Results of titrimetric determination of Hydroxyzine dihydrochloride in model solutions using Oxone ($n = 7$; $P = 0.95$)

Taken HDH, mg	Found HDH $\pm \Delta$ (mg)	RSD, %	Accuracy (%), $\delta = \left(\frac{\text{Found} - \text{Taken}}{\text{Taken}} \right) \cdot 100\%$
2.24	2.25 \pm 0.05	2.50	-0.45
4.48	4.51 \pm 0.06	1.49	+0.67
8.96	8.97 \pm 0.07	0.87	+0.11
22.40	22.41 \pm 0.10	0.43	+0.05

* μ is true content of HDH (taken) (mg)

Results of titrimetric determination of the content of the main substance in the substance Hydroxyzine dihydrochloride using Oxone are given in Table 2. $RSD = 0.45\%$. $\left| \left(\frac{\text{Found} - \mu}{\mu} \right) \cdot 100 \right| < RSD$

Table 2
Results of titrimetric determination of the content of the main substance in the API HDH substance using Oxone ($n = 7$; $P = 0.95$)

content indicated in the Certificate analysis (w, %)	Found $(\pm \Delta)$, (%)	RSD, %	Accuracy (%), $\delta = \left(\frac{\text{Found} - \text{Indicated}}{\text{Indicated}} \right) \cdot 100\%$
99.6*	99.2 \pm 0.44	0.45	-0.40

* Average HDH content data of the official method BPh, μ

The results of the analysis of ATARAX® tablets, 25 mg each according to the proposed method ($n = 5$; $P = 0.95$) are shown in Table 3. $RSD \leq 1.52\%$. $\left| \left(\frac{\text{Found} - \mu}{\mu} \right) \cdot 100 \right| < RSD$.

Table 3

The results of the analysis of ATARAX® tablets, 25 mg each according to the proposed method ($n = 5$; $P = 0.95$)

Active substance, analyte	Found ($\pm \Delta$), mg/ tabl. Percentage of declared (% Recovery)	RSD, %	Average content analysis certificate data (μ^*) mg/tab.	Accuracy, ($\frac{\mu^* - \mu}{\mu}$) (%)
<i>Hydroxyzine - ATARAX® film-coated tablets</i> 25 mg; Series N° 313517 Manufacturer USB Pharma S.A., Belgium	25.10 \pm 0.38 <i>RE</i> = 100.4 \pm 1.5	1,52	24.63 (98.5%)	+ 0.50
* Data from official BPh method, μ				

Conclusions

The kinetics of the oxidation reaction of hydroxyzine hydrochloride with potassium hydrogen peroxomonosulfate was studied depending on the pH of the medium. It has been established that the reaction kinetics obeys the general laws of specific acid-base catalysis. Techniques have been developed and the possibility of quantitative determination of Hydroxyzine hydrochloride in the substance and tablets of 25 mg by iodometry using Oxone as an analytical reagent has been shown. $RSD \leq 1.52\%$. $\delta < RSD$.

Declarations

Funding

No funding was received.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval and consent to participate

Not applicable.

II and MB conducted the experiments and analyzed the data. VY, VM, OK assisted in the experiments and discussed the results. MB and II wrote the manuscript and drew the graphs. VM, OK revised the manuscript. All authors read and approved the final manuscript.

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Figures

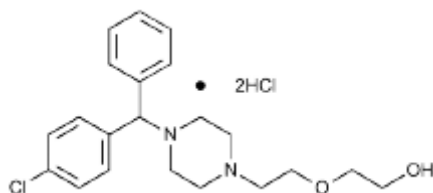


Figure 1

Chemical Formula of Hydroxyzine Dihydrochloride

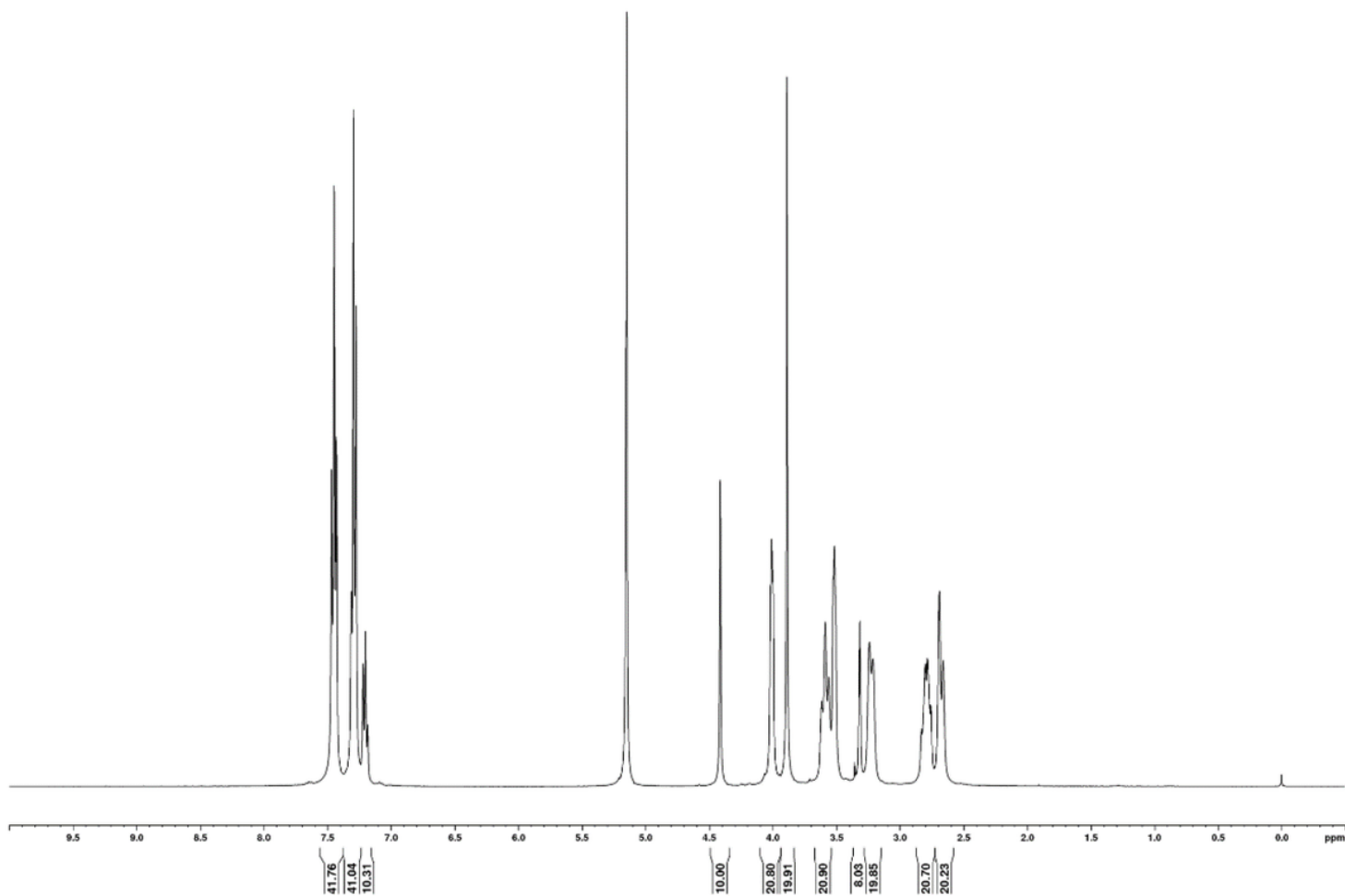


Figure 2

The Proton NMR Spectrum of isolated Hydroxyzine oxidation product

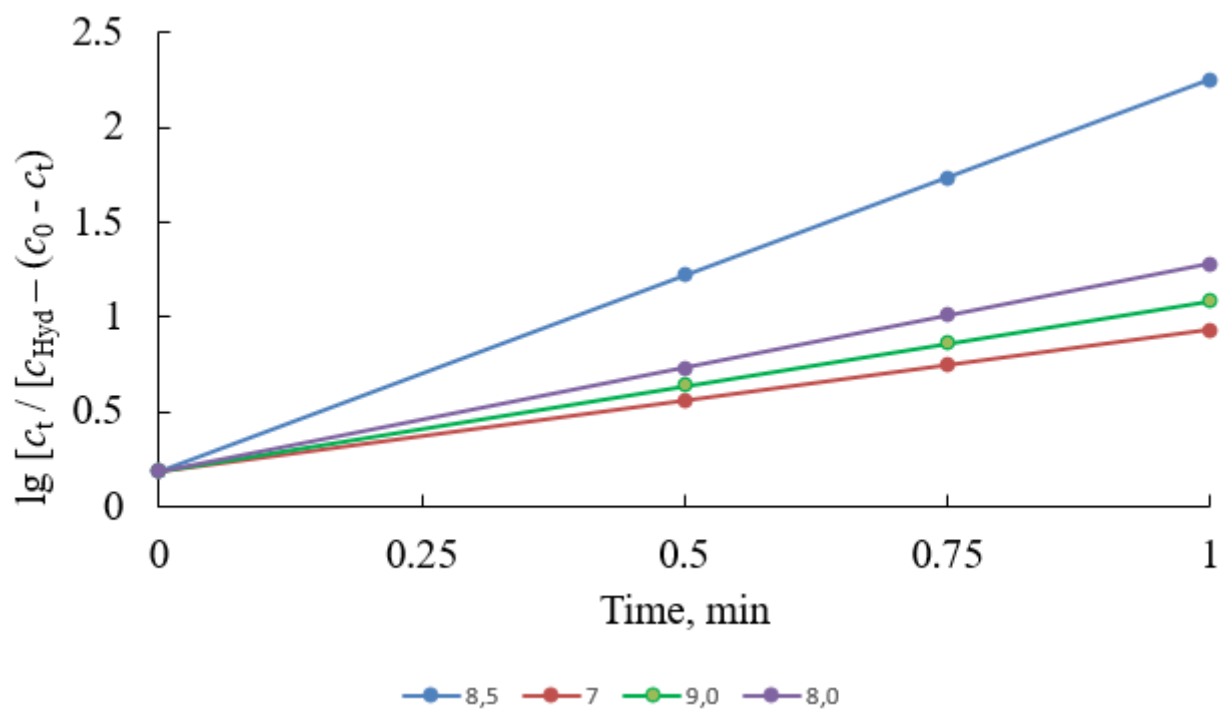


Figure 3

Semi-log anamorphoses of kinetic reaction curves N-oxidation of hydroxyzine with potassium hydrogen peroxomonosulfate depending on the pH.

$$c(\text{Hyd}) = 1.35 \cdot 10^{-3} \text{ mol l}^{-1}; c(\text{KHSO}_5) = 2.05 \cdot 10^{-3} \text{ mol l}^{-1}$$

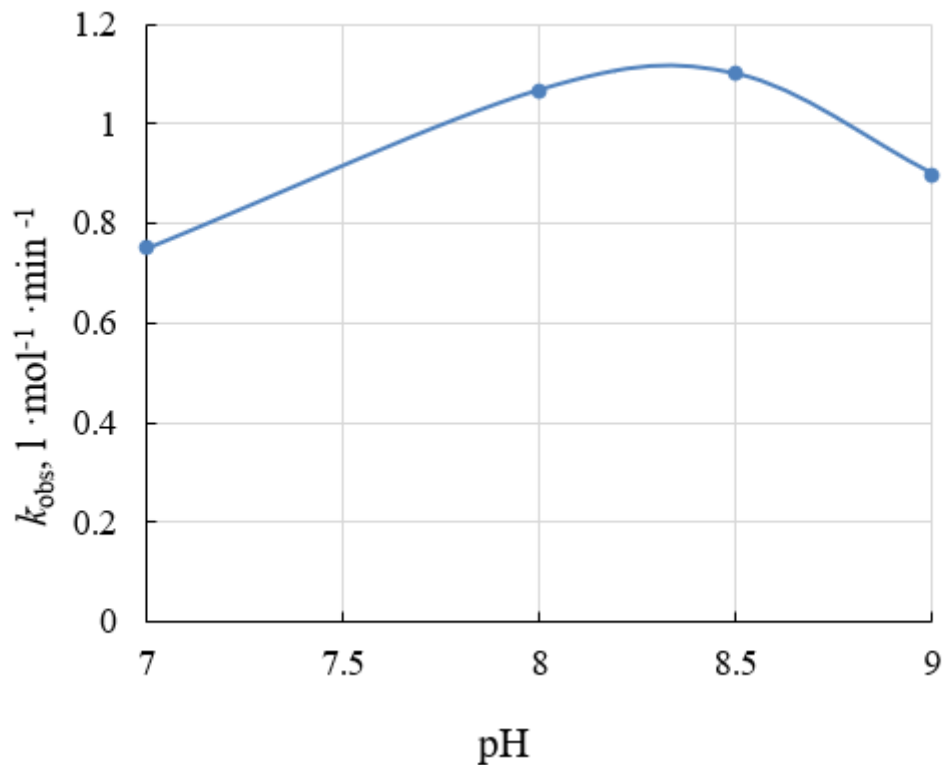


Figure 4

The dependence of the observed second-order constant of the reaction of N-oxidation of Hydroxyzine with potassium hydrogenperoxomonosulfate on the pH of the medium

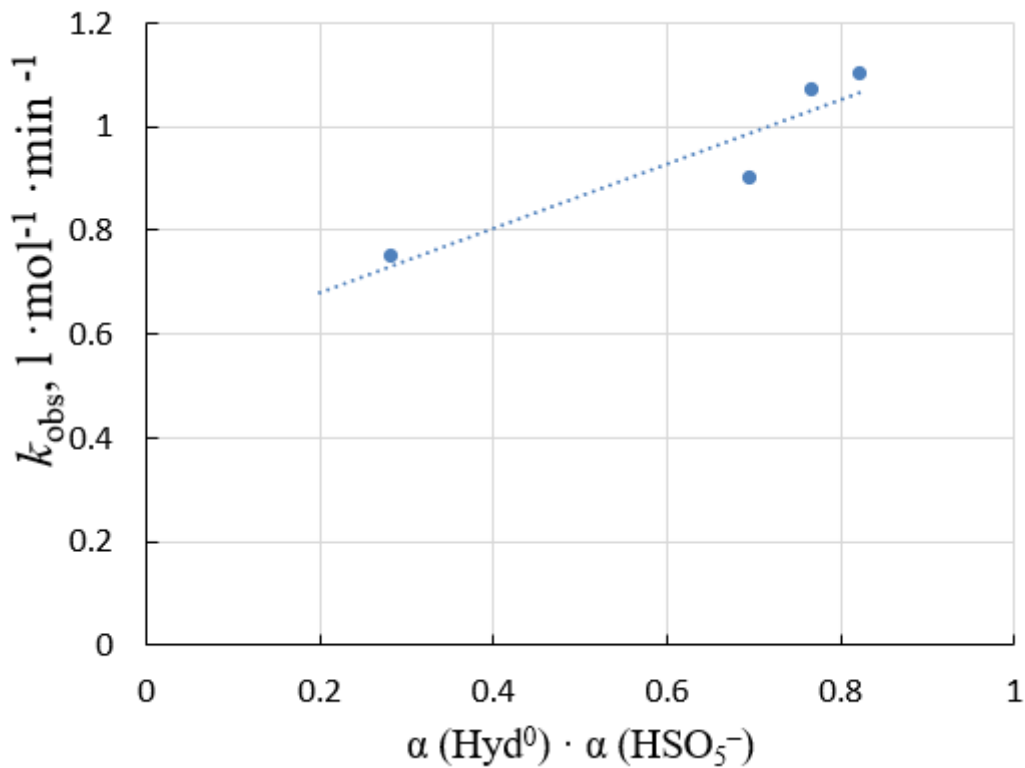


Figure 5

Dependence of the observed second-order rate constant (k_{obs}) of the reaction of *N*-oxidation of Hydroxyzine with potassium hydrogen peroxomonosulfate on the product of the molar fractions of the Hydroxyzine base and the HSO_5^- monoanion

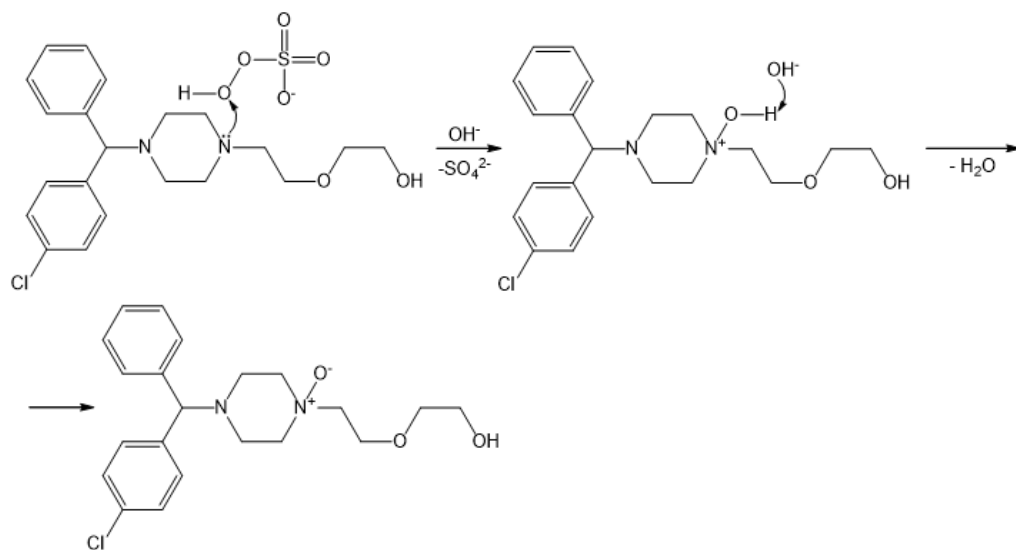


Figure 6

Scheme of the oxidation process of Hydroxyzine with potassium hydrogen peroxomonosulfate