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A study of the photodegradation kinetics of yohimbine in acid media using multivariate curve resolution alternate least square (MCR-ALS)

A.E.El Gendy[1], M.Farouk[2], L.Abd El Aziz[2]*, A.Ashour[1], E.S.Shokry[1]

[1]Faculty of Pharmacy, Misr International University, Cairo, (EGYPT)

[2]Faculty of Pharmacy, Ain Shams University, Cairo, (EGYPT)

E-mail : labna.analytical@yahoo.com

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ABSTRACT

A multivariate curve resolution method based on combination of multivariate curve resolution and alternate least square (MCR-ALS) is presented. The proposed method was used to study the degradation kinetics of yohimbine sulphuric acid solution upon exposure to the light of an 8-watt UV lamp in the range of 254 nm. The spectra of YOH in different concentrations of acid solutions collected at different lighting times (5 minute interval) were subjected to factor analysis and three different components were detected in the reaction system. Pure spectra of the components involved and their concentration profiles were obtained. It was suggested that in the presence of light, the acid solutions of YOH are sensitive to atmospheric oxygen and they oxidize to 3,4 dehydroyohimbine. A two step mechanism is proposed for this photochemical reaction. In the first step, excited YOH reacts with ground state oxygen to give hydroperoxoyohimbine. This intermediate slowly rearranges in a second acid catalyzed step to yield 3,4 dehydroyohimbine. The results revealed that the photodecomposition of YOH and the formation of dehydroyohimbine (DH) follow first order kinetics whose rate constants increase linearly with the concentration of acid.

INTRODUCTION

Spectroscopy has been applied as a useful, highly sensitive tool for the study of chemical reactions in solutions, one of which is photodegradation, where if the components involved in the chemical reactions have distinct spectral responses, their concentrations can be monitored directly, but in many cases, the spectral responses of two, sometimes, even more components overlap considerably and the analysis is no longer straight forward.

The common approach has been the single point measurements at a wavelength where one component dominates the spectral response and the contributions from the other components are neglected. However by the use of chemometrics methods[1], one can analyze the whole spectral, thereby utilizing all spectral information. This approach is superior to any single point measurement since several hundreds of data points can be treated simultaneously. Multivariate curve resolution or spectral curve deconvolution can be defined as a group of techniques which help resolve mixtures by determining the number of constituents, their response profiles (spectra, PH profiles, time profiles, elution profiles, ….) and their estimated concentrations, when no or little prior information is available about the nature and the composition of these mixtures.

The theory of multivariate curve resolution alternate least square method mathematically speaking, a principal component analysis (PCA) and multivariate curve resolution alternate least square methods were proposed in this study. Both approaches assume a bilinear model

to explain the observed data variance using a reduced number of components as given in equations (1,2):

$$d_{ij}(\lambda) = \sum_{n=1}^{N} C_{in} S_{nj}(\lambda) + e_{ij} \; (j = 1, n) \quad (1)$$

$$D = CS^T + E \quad (2)$$

In Equation (1) d_{ij} refers to the data measurement (response) of variable j in sample i, N are the number of components (species), C_{in} is the concentration of component n at variable j, S_{nj} is the contribution considering the total number of n = N components. This equation means that the measured concentrations are a weighed (Scores, C_{in}) Sum of a reduced number (N) of main contributions defined by a particular chemical composition (loadings S_{nj}) a part from noise (multiple small known contributions, and experimental error defined by e_{ij}.

In other words, the weights or scores (C_{in}) describe how the main components are distributed among the analysed samples, and the loadings (S_{nj}) identify the chemical composition of these components. When this linear equation is written in a matrix form (equation 2), (D) is the matrix of measurements where the rows of matrix D are the spectra measured during the experiment, the column profiles of matrix C which is the matrix of scores (distribution of components of the reaction mixture among samples), the row profiles of S^T where S is the matrix of loadings (composition of the components of the reaction mixtures), the superscript T means the transpose of matrix S, where pure spectra are column profiles, E is the matrix of residuals not explained by the model and ideally should be close to the experimental error.

Note that Equation (2) is the multi-wavelength extension of Beer's-Lambert law in matrix form.

The goal of MCR-ALS is the bilinear decomposition of the data matrix D into the "true" pure response profiles associated with the variation of each contribution in the row and the column directions represented by matrices C and S^T respectively which are responsible for the observed data variance.

The PCA model can be described in equations (3-5)

$$D = UV^T + E \text{ (PCA model)} \quad (3)$$

$$D = U^* SV^T + E \text{ (SVD Model)} \quad (4)$$

$$Si, i = \sqrt{\lambda} = \lambda^{1/2} \quad (5)$$

Where in equation (3) U is the scores matrix (orthogonal), V^T is the loadings matrix (orthonormal) and in equation (4) representing singular value decomposition model (SVD model).

U* is the scores matrix (orthonormal), S is the diagonal matrix of the singular values where the magnitude of the singular value reflects the importance of contribution, λ refers to the eigen values of the covariance matrix DD^T, V^T refers to the loading matrix (orthonormal) and according to PCA..

$$D = UV^T + E$$

Or

D = Structure + noise.

Loadings (Projections): V^T refers to relationship between original variable and the principal components (eigen vectors of the covariances matrix), where vectors in V^T (loadings) are orthonomrals (orthogonal and normalized).

Scores (Targets): U refers to relationships between the samples (coordinates of samples or objects in the space defined by the principal components, where vectors in U (scores) are orthogonal, E is the noise, or experimental error (non explained variances).

As for MCR-ALS, it solves iteratively Eq. (2) by an alternating least square algorithm which calculates concentration (C) and pure spectra (S^T) matrices optimally fitting the experimental data matrix D in order to recover how components of the reaction mixture are really in physical terms (loadings) and how they are really distributed among samples (Scores).

This optimization is carried out for a proposed number of components and using initial estimates of either C or S^T.

The initial estimates of C or S are obtained from pure variable detection methods and optional constraints are applied at each iteration as shown in equations (6,7).

$$S^T = C + \hat{D}_{PCA} \quad (6)$$

$$C = C + \hat{D}_{PCA} \; (S^T)^+ \quad (7)$$

Where C, $(S^T)^+$ are the pseudoinverses of C and S^T respectively.

ALS optimizes concentration and spectra profiles using a constrained alternating least square method. The main steps of the method are:

1. Calculation of the PCA reproduced data matrix.
2. Calculation of initial estimates of concentration or spectral profilers.

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3. Alternating least squares including:
   - Iterative least squares constrained estimation of C or S^T.
   - Iterative least squares constrained estimation of S^T or C.
4. Interpretation of results.

In the present work, (MCR-ALS) was applied as a computer assisted chemometrics for the study of the kinetics of photodegradation of YOH.HCl. The spectral data, recorded under the light of an 8-watt lamp in the 5 min. intervals were collected in five data matrices (a data matrix D for each acid concentration) each with mxn dimension, m being the number of data points per spectrum, n being the number of spectra collected at various reaction times, if there are N absorbing components in the reaction system, the recorded absorbance is the sum of contributions of all components.

EXPERIMENTAL

Instrumentation

All spectra were recorded on a Shimadzu UV-1650 double beam spectrophotometer connected to a computer loaded with Shimadzu Software, UV-probe 2.10 was used (Hiroshima, Japan). UV spectra were recorded using a 1 cm quartz cell, the scan range was 200-400 nm with 0.2 nm intervals.

A multivariate curve resolution program was written in MATLAB Vers. .5, the Math Work Inc.).

Samples and reagents

Authentic samples

Yohimbine hydrochloride certified to contain 99.90 % by the manufacturer method was kindly supplied by Al-Amriya Pharmaceuticals (Alexandria-Egypt).

Reagents

Sulphuric acid (Adwic, Egypt) used was of analytical spectroscopic grade and obtained from (Adwic, Egypt) company.

Distilled water was used for the preparation of 0.5 M, 1M, 1.5 M, 2 M, 2.5 M H_2SO_4 acid.

Standard stock solution for yohimbine hydrochloride

A stock solution of Yohimbine hydrochloride (YOH.HCl) was prepared by transferring 10.0 mg of YOH in a 100 ml volumetric flask and dissolving it in a minimum amount of water, sonicating for 10 minutes, then the volume is made up to the mark with the same solvent to give a final concentration of 100.0 μgml^{-1}.

Standard working solutions for yohimbine hydrochloride

Appropriate dilutions are done to prepare a 20.0 μgml^{-1} solution of YOH. HCl in 0.5M, 1 M, 1.5 M, 2 M, 2.5 M H_2SO_4 acid.

Procedure

Irradiation test

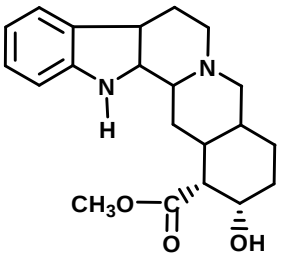
The irradiation test employed utilized an 8-watt lamp placed 50 cm from the YOH solution placed in a 1 cm quartz cuvette. Irradiation was conducted in side a dark room to protect samples from extraneous light. The UV-Vis. Spectra of solutions (200-400 nm) were recorded in 5 min intervals up to 120 min.

Application of multivariate curve resolution analysis

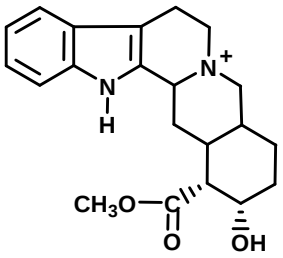
The obtained absorbance spectra of each of the solutions were collected in a data matrix (D), the five data matrices were subjected to the multivariate curve resolution analysis. From the resulted concentration profiles of the components in each matrix. The reaction rate constants were calculated at each acid concentration.

RESULTS AND DISCUSSION

Because YOH contains in its basic structure the indole ring[2], it possesses physicochemical properties similar to those observed in simplest indoles, nevertheless as in case of the other Rauwolfia alkaloids, the presence of the piperidinic ring in tehse molecules confers them a distinctive behavior. Thus, although Rauwolfia alkaloids oxidize to give reaction products structurally similar to these reported for other indolic compounds[3,4], they can be also aromatized derivatives. The last oxidation reactions have a special interest, because apart from being specific of these alkaloids they can be used for their quantitative determination. Interestingly, while in the chemical oxidation of YOH by different oxidizing agents in acid media, its partially aromatized derivative 3,4-dehydroyohimbine (DH) has been reported as the sole oxidation product[5-8].



Yohimbine (YOH)



3,4 -dehydroyohimbine (DH)

This compound is formed only by the chemical oxidation of YOH in acid media, thus an acid medium is needed for DH to be formed[9-12]. In fact, to our experience DH is the usual photooxidation product of the acid aqueous yohimbine solutions long standing at the laboratory day light[5,6,9-12].

The appearance of DH in these solutions is clearly recognizable by the presence of absorption band at 300 nm in their UV absorption spectra. Moreover this type of dehydroderivative is a well known photo-oxidation product of the structurally related alkaloid reserpine[4,6].

The aim of this part is to study the degradation kinetics of YOH and the effect of the acidity (strength of the acidic medium) on the rate of the reaction.

Figure 1 shows the spectra of Yohimbine in 1M H_2SO_4 acid collected at 5 min. intervals upon exposure to UV light at 254 nm at 25°C, as it is shown that yohimbine possesses a weakly structural band with a maximum absorption in the 270-290 nm region[7]. This band embodies the structural characteristics of the indole chromophore which disappears gradually upon exposure to light accompanied by the appearance of a new band at 354 nm which in turn disappears gradually, concomitant with the appearance a growing bands at 250 nm and 300 nm.

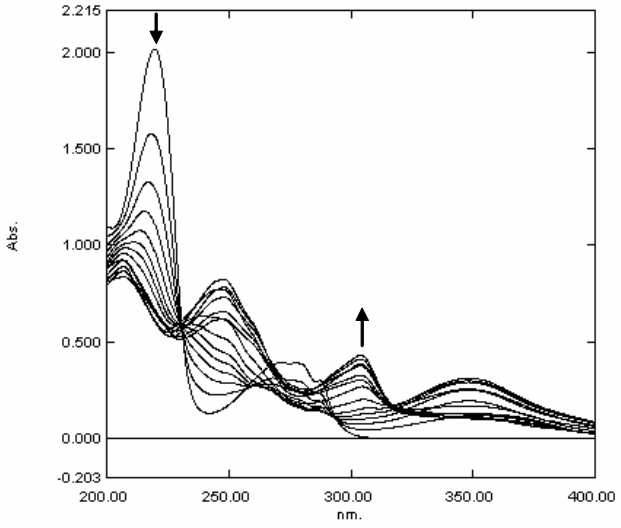


Figure 1 : Absorption spectra of yohimbine hydrochloride in 1 M sulphuric acid at different lighting times collected at 5 minute intervals.

In order to resolve YOH and its degradation products, the MCR procedure was conducted, thus the resulting absorbance data matrix was subjected to PCA to find the number of chemical components coexisting in the system. The results are plotted in figure 2, 3. In figure 2, the evolution of the eigen values is plotted as a function of the number of factors. The large change observed between the eigen values is plotted as a function of the number of factors. The large change observed between the eigen values 3 and 4 emphasize that three components are involved in the process. Furthermore, loading plot would also provide an estimation of the number of significant components or factors present in the system as shown in figure 3. The scores plot reveals three components which area; the intact drug (Figure 4a), intermediate (whose concentration increases gradually along with

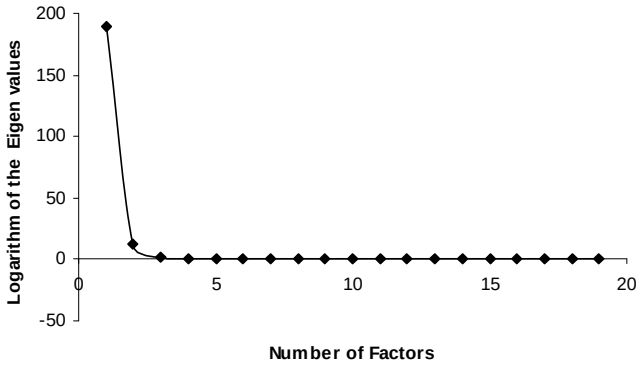


Figure 2 : Plot of the logarithm of eigenvalue as a function of the number of factors.

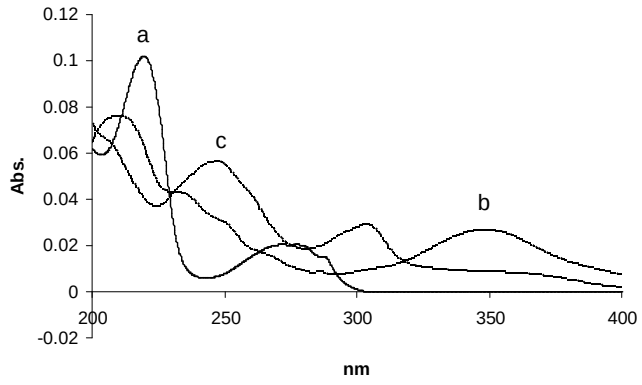


Figure 3 : Plot of the loadings obtained from the absorbance data matrix of yohimbine hydrochloride (a), indolenine intermediate (b), and the photodegradate (c) resulted after convergence of MCR-ALS.

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the decrease in the concentration of the intact drug, then its concentration decrease gradually (Figure 4b, 4c), along with the formation of the final product), and the third component is the final reaction product (DH) whose concentration increase gradually with time (Figure 4d).

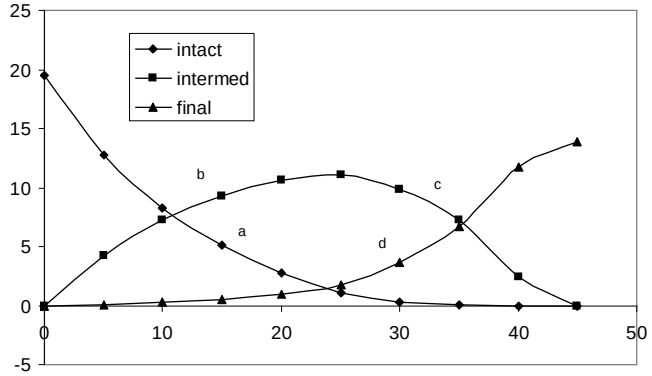


Figure 4 : Plot of the scores obtained from the absorbance data matrix of yohimbine hydrochloride (a), indolenine intermediate (b) and the photodegradate (c).

The pure spectra of the components and their corresponding concentration profiles were determined by MCR-ALS. It was observed that the resolved spectra of YOH, intermediate and final reaction product (DH) are similar to those obtained experimentally as shown in figure 3, 5.

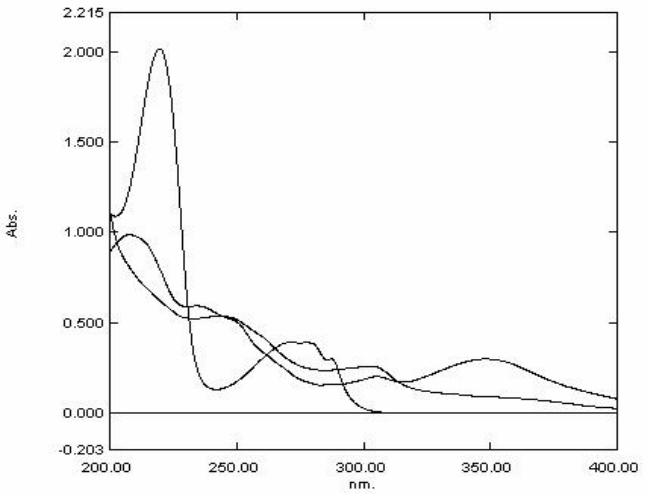


Figure 5 : Optimum pure spectra of yohimbine hydrochloride, indolenine intermediate, and the photodegradate.

According to Einstein photochemical equivalence law the kinetics of such reaction is first order (-dc/dt = KC) i.e., under such acidity conditions, both the disappearance of YOH, K_{obs1} and the formation of DH, $K_{obs.2}$ increase linearly with the increase in the acid concentration. Thus, the rate of the reaction (K) and the half life ($t_{1/2}$) of the reaction can be calculated form the equations:

Ln C = Ln C – Kt

$t_{1/2} = 0.693/ K_{obs}$

and the results are presented in figure 6. From the results, it was observed that $K_{obs.1}$ is always greater than K_{obs2}, this means that the kinetic processes are not coupled i.e., DH is formed through a two step mechanism involving a long lived intermediate (hydroperoxoindolenine)[13-15] as shown in Scheme 1.

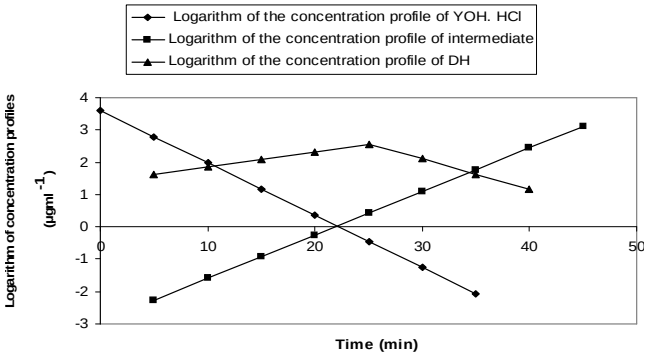
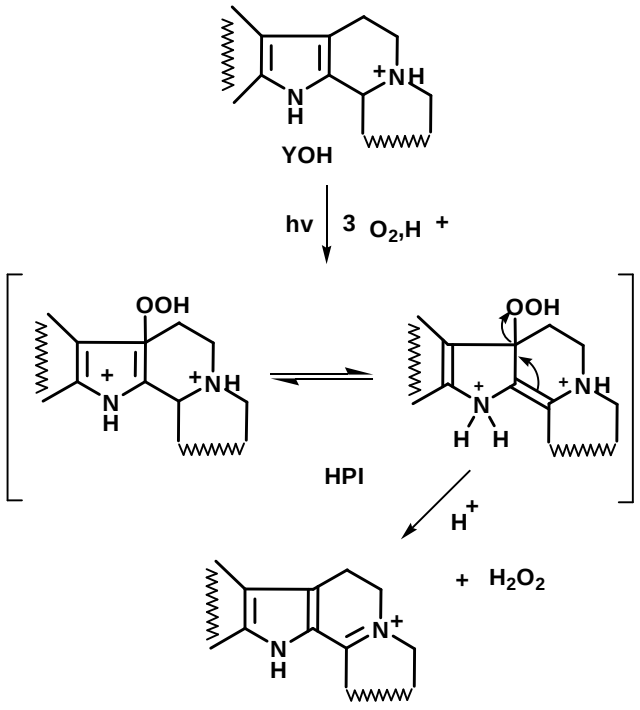


Figure 6 : Plot of the logarithm of the concentration profiles of yohimbine hydrochloride and its photodegradate versus time after convergence of MCR-ALS.



Scheme 1

In order to study the effect of the concentration of sulphuric acid on the reaction rate, experiments were

performed using different acid concentrations (0.5M, 1M, 1.5M, 2M, 2.5M). Figures 7, 8 shows that both the degradation of YOH and the formation of DH are first order reactions whose rates are strongly dependent on the acid concentration, and that was confirmed by plotting the reaction rate constants as a function of the acid concentration and the plots was found to be linear according to the equation:

$$K_{obs} = K_0 + K_1 [H^+]$$

Where K_0 is the intercept and $[H^+]$ is the acid concentration, and the values of the slopes, intercepts, and regression coefficient of the K_{obs} versus sulphuric acid plots at different acid concentration are listed in TABLE 1.

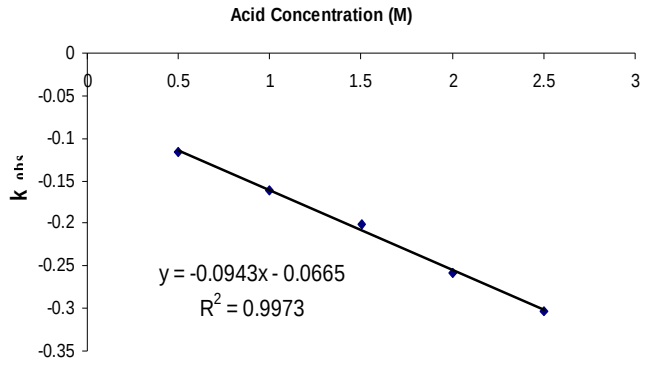


Figure 7 : Plot of the slopes of the logarithm of the concentration profiles of yohimbine hydrochloride versus different concentrations of sulphuric acid.

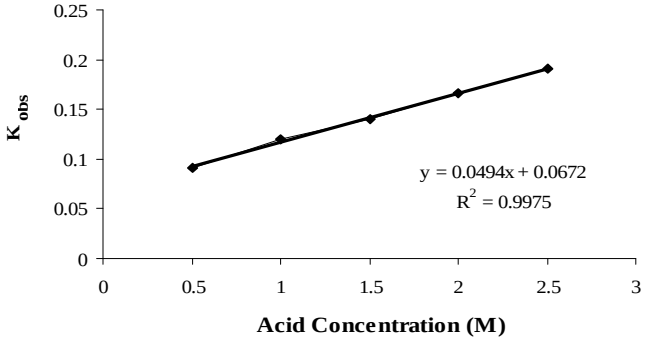


Figure 8 : Plot of the slopes of the logarithm of the concentration profiles of dehydroyohimbine versus different concentrations of sulphuric acid.

TABLE 1: Values of the slopes, intercepts, and regression coefficient of the K_{obs} versus sulphuric acid plots at different and concentration.

	Slope	Intercept	Regression coefficient (r)
Breakdown of intact	-0.0943	-0.0665	0.9987
Formation of degradate	0.0494	0.0672	0.9988

CONCLUSION

A multivariate curve resolution method coupled with an alternate least square approach was applied to study the kinetics of photodegradation of yohimbine hydrochloride upon exposure to an 8-watt lamp in a sulphuric acid medium. Factor analysis showed that there are three chemical components in the reaction system; yohimbine, the hydroperoxoindolenine intermediate, and the final product which is the dehydroyohimbine (DH), the resulting concentration- time profile of the componenets showed that the disappearance of YOH and the formation of DH follow first order kinetics whose rate constants increase linearly with the concentration of acid. A two step mechanism is proposed for this chemical reaction.In the first step excited yohimbine reacts with ground state oxygen to give hydroperoxoindolenine. The intermediate slowly rearranges in a second acid catalysed step to yield 3,4-dehydroyohimbine.

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