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Evolution of Thermodynamic and Structural Properties of Coumarins by Molecular Dynamics Simulation

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ABSTRACT

Molecular simulation provides an intermediate method between experiments and classical models. It has given useful predictions to understand the relation property-chemical structure. In this work, we have studied the evolution of thermodynamic and structural properties. We have used the Lennard-Jones potential model in the simulation calculation. Our aim is to determine the properties of 7-hydroxy-4-methyl coumarin and 5,7-dihydroxy-4-methyl coumarin using molecular dynamics. This method provides an advantage to confirm the structure-activity relationship for these compounds. We have calculated the thermodynamic and structural properties for both the NVT and NPT ensembles of hydroxy derivatives of 4-methyl coumarin. Our simulation model in NPT system gives precise results and approaches very well the experimental data.

Key words: Coumarins, molecular dynamics, radial distribution function, thermodynamic properties.

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INTRODUCTION

Coumarins are heterocyclic organic compounds. They are known as benzo-2-pyrone derivatives, mainly found in plants of the family of Rutaceae and Umbelliferae. Coumarins can be obtained from the plants by different extraction methods such as Maceration under sonication, infusion and supercritical fluid extraction [1]. These compounds have been attracting great interest because of their importance in synthetic organic chemistry. Many of their analogues have found application in pharmaceuticals, fragrances, agrochemicals, and insecticides [2-5].

Hydroxy derivatives of 4-methyl coumarin are important group of coumarin derivatives showing medicinal as well as other applications, as optical brightening agents, dispersed fluorescent and tunable dye lasers [6]. The 7-hydroxy-4-methyl coumarin is used as fluorescent brightener, and efficient dye lasers [7], as a starting material for the preparation of Hymecromone [8] (figure 1).

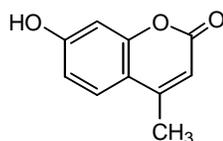


Figure 1 : Structure of 7-hydroxy-4-methylcoumarin.

In this work, we have studied the evolution of thermodynamic and structural properties for 7-hydroxy-4-methyl coumarin and 5,7-dihydroxy-4-methyl coumarin. We have used the Lennard-Jones potential model in the molecular dynamics simulation. This method provides an advantage to confirm the structure-activity relationship for these compounds. We have calculated the thermodynamic and structural properties for both the NVT and NPT ensembles of hydroxy derivatives of 4-methyl coumarin.

In section 2, we have cited the different methods used in the synthesis of coumarins and proposed the mechanism of Pechmann reaction. In the next section, structure-activity relationship is described and discussed. In section 4, we have detailed the molecular dynamics simulation : i) potential model of interaction, ii) structural properties, and iii) thermodynamic properties. Section 5 is reserved to study our compounds in canonical and isothermal-isobaric systems and to determine the structural and thermodynamic properties for both the systems. We give the comparative calculations with the spectroscopic analysis and the comparative thermodynamic properties of coumarins in section 6. In the last section we give the conclusion.

Synthesis of coumarin

Chemically, coumarins can be synthesized by various methods such as the Perkin [9], Pechmann reaction [10], Knoevenagel condensation [11], Reformatsky [12], Wittig [13], Claisen rearrangement [14] and catalytic cyclization reactions [15]. Acid catalyzed Pechmann reaction is the simple and commonly used method for synthesizing coumarins from activated phenols, mostly m-substituted phenols containing electron donating substituent at m-position and β -keto-esters or an unsaturated carboxylic acid. The Pechmann reaction proceeds through three steps: transesterification and intramolecular hydroxyalkylation, followed by dehydration [16]. This reaction depends on Bronsted acidity of catalyst. So, we propose the mechanism taken from literature [17] (figure 2).

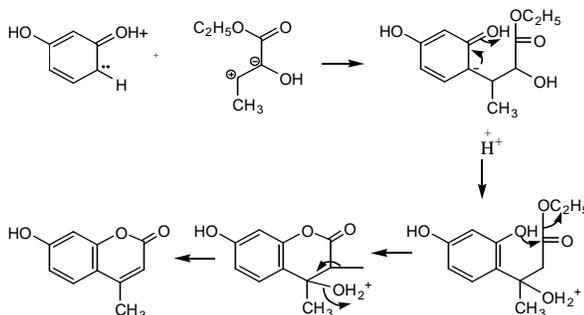


Figure 2 : Proposed mechanism for the synthesis of coumarin.

Structure-Activity relationship

In the Pechmann reaction, the electron-donor substitutes can enhance the activity when in meta position and diminish the reactivity of the phenol when in ortho or para positions.

The reactivity of phloroglucinol with ethyl acetoacetate was observed to be higher than pyrogallol due to two hydroxy groups at meta-positions in phloroglucinol compared to one hydroxy group in pyrogallol. Presence of meta-hydroxy group strongly activates the substrates due to resonance effect. However, phenol and m-methyl-phenol are less reactive due to absence of any activating group in phenol; and presence of weakly activating methyl group in m-methyl phenol.

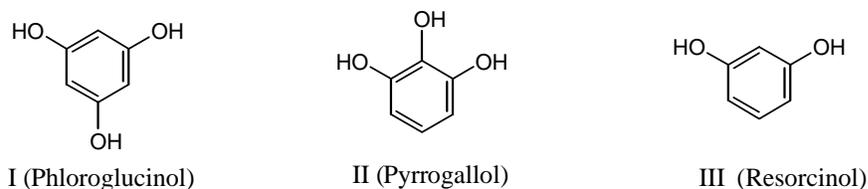


Figure 3 : Phenol derivatives.

Reactions of 1,3,5-trihydroxybenzene with ethyl/methyl acetoacetate took place very fast (4 to 5 min). This is mainly due to the presence of three hydroxyl groups that cooperate in activating the aromatic ring for hydroxyalkylation [18,19]. Similarly, reactions of 1,2,3-trihydroxybenzene with ethyl/methyl acetoacetate took place in 25 to 15 min, which are slower than that of the reactions of 1,3,5-trihydroxybenzene presumably due to steric hindrance of hydroxyl groups [20]. However, the reactivity of 1,3-dihydroxybenzene with ethyl/methyl acetoacetate diminished rapidly (143 to 77 min) [20,21]. This could be due to the presence of only two hydroxyl groups, which are meta to each other (figure 3) [22].

We find similar results in the biological activity. The coumarin resulting from isomer I is more active than the others [23].

Molecular Dynamics simulation

Potential model

In literature, many potentials are proposed [24-26]. The first potential having a theoretical significance is the inverse potential [27]. Hoover have used the 9,6, and 4 inverse potentials to study the transition phase fluid-solid [28]. After, the searchers have employed the square well potential [29]. Consider its insufficiency, scientists have preferred Lennard-Jones potential for the spherical interactions [30] and Buckingham potential for the site-site interactions [31,32]. There are two other potentials : Exponential-6 [33], and Kihara [34] which are recommended in the spherical interaction studies [35].

To model the particle interactions, we have used the classical Lennard-Jones model. The depth of attractive well ϵ and the effective diameter interaction σ are the two characteristic parameters of the LJ potential. This potential has been frequently used to describe the non-bonded energy interaction between molecules (Eq 1).

$$U_L(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right] \quad \text{Eq 1}$$

Where r is the distance between the center of mass of molecules.

In table 1, we give the physical properties of coumarins. These ones are used in the molecular dynamics experiences in both NVT and NPT systems.



Physical properties	C ₉ H ₆ O ₂	C ₁₀ H ₈ O ₃	C ₁₀ H ₈ O ₄
Melting point (°C)	69-71	183-186	282-285
Composition (% mol)	0.3425	0.5632	0.7851
Molar weight (g/mol)	146.15	176.17	192.17

Table 1 : SPx points used in Molecular Dynamics simulation in both NVT and NPT ensembles for coumarins.

In this study, the numerical simulation calculation is obtained from Gear Predictor algorithm using the LJ potential model. We have described the radial distribution functions and determined the properties of 7-hydroxy-4-methyl coumarin and 5,7-dihydroxy-4-methyl coumarin. We have also studied the evolution of the thermodynamic properties for coumarins. We have taken 20 molecules in the MD box. Only molecules of pure compound are considered in the spherical intermolecular interactions.

The periodic boundary conditions around the central cubic box and the minimum image truncation were included in the calculations. Long-range corrections are also applied. The equations of motion (both for the translation and rotation) are solved using the Maxwell-Boltzmann distribution. The overall runtime is 250 ps with an equilibration period of 50 ps and data production period reaching up to 50 ps to ensure a good accuracy in calculated ensemble averages of most properties.

Structural Properties

The correlation function $g(r)$ is proportional to the probability density of finding the α site in molecule 1 at a distance $r_{\alpha\beta}$ from the β site in molecule 2. It is given in terms of the angular pair correlation function [30, 32,33]. The equation of $g(r)$ can be easily obtained from equation cited in reference 33.

$$G(r_{\alpha\beta}) = \langle g(r_{\alpha\beta} + r_{c\alpha 1} - r_{c\beta 2}; w_1 w_2) \rangle_{w_1 w_2} \quad \text{Eq 2}$$

Where $\langle \dots \rangle_{w_1 w_2}$ is an outweighed average over the molecular orientations.

The structural properties $g(r)$ are calculated to describe the structure of the compound, when the system has attained the equilibrium.

$$g(r) = \left(\frac{V}{N} \right) \frac{N(r, r + dr)}{4\pi r^2 dr} = \frac{N(r, r + dr)}{4\pi \rho r^2 \Delta r} \quad \text{Eq 3}$$

Where $N(r, r+dr)$ represents the particle number in the spherical covering (with radius r). In equation 3, the denominator is used to normalize the average of this material quantity.

Thermodynamic Properties

The total energy of a molecular system is the sum of its kinetic energy (translation and rotation), KT and KR , and its potential energy U :

$$ET = (KT + KR) + U \quad \text{Eq 5}$$

$$KT = \frac{1}{N} \sum \left[\sum \left(m_i \frac{v_i^2}{2} \right) \right] \quad \text{Eq 6}$$

$$KR = \frac{1}{N} \sum \left[\sum \left(I \frac{\omega_i^2}{2} \right) \right] \quad \text{Eq 7}$$



$$U = \frac{1}{N} \sum [\sum \sum (U(r_{ij}))] \quad \text{Eq 8}$$

$$ET = \frac{1}{N} \sum \left[\sum \frac{m_i v_i^2}{2} + \sum I \frac{w_i^2}{2} + \sum \sum (U(r_{ij})) \right] \quad \text{Eq 9}$$

Where m is the masse of particle i, v the speed, I inertia moment, and w angular speed.

In molecular dynamics, the solution of the equations of motion allows to compute the kinetic energy at each time. The average kinetic energy is used to determine the temperature of the system. It is essential to compute the potential energy from molecular coordinates. Typically, it is decomposed into intermolecular (or external) energy and intramolecular energy. In this study, we consider only the intermolecular energy.

Due to the theorem of equipartition, the temperature is linked to the kinetic energy and determined when the system has reached the equilibrium (Eq 10). Temperature remains stable during the simulation time and fluctuate around the average value of 0.6287 (reduced unit).

$$T = \frac{1}{3NK_B} \sum \left[\frac{1}{N} \sum (m_i v_i^2) + (I w_i^2) \right] \quad \text{Eq 10}$$

The pressure is obtained from the virial theorem (Eq 11) [36] and be constant at the showed temperature.

$$P = \frac{2}{3V} E_c - \frac{1}{3VN} \sum \left[\sum \sum \left(r \frac{\partial}{\partial r_{ij}} U(r_{ij}) \right) \right] \quad \text{Eq 11}$$

Where ∂ is the virial coefficient and V the complete volume.

RESULTS AND DISCUSSION

Canonical system (NVT)

Structural Properties

For the point Sp1, the radial distribution function becomes zero at short distances, where repulsive forces prevent overlapping of molecules. When r is close to the collision diameter σ , g(r) raises rapidly to a maximum corresponding to the first peak. As r increases, it decreases at the long range and keeps to 1. This situation is the characteristic of the liquid state (figure 4). Compound $C_{10}H_8O_4$ has the maximum equal to 0.57σ due to the existence of two attractor-effect (OH) and one electron-donor effect (Me). The intensity is diminished with the number of substituents. Compound $C_{10}H_8O_3$ presents a peak equal to 0.47σ , and reference coumarin provides a peak equal to 0.37σ . Correspondingly, the intermolecular interactions (type H bond) are numerous for $C_{10}H_8O_4$ than in case of $C_{10}H_8O_3$. These interactions are absents for the reference coumarin.

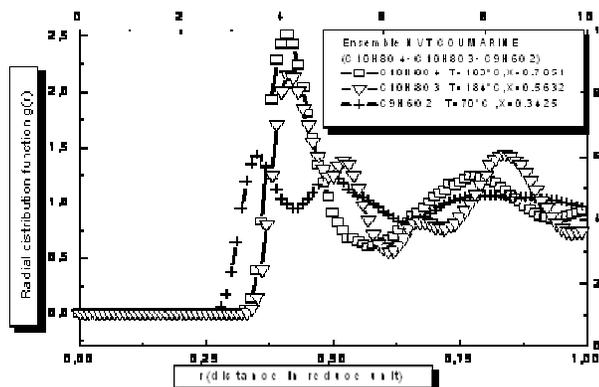


Figure 4: Radial distribution functions of coumarins in NVT ensemble at the point Sp1.

Thermodynamic Properties

The total energy arises from the interaction between different molecules and becomes more high for the $C_{10}H_8O_4$ compound. In reduced unit, the value of U is equal to 0.0324 (figure 5).

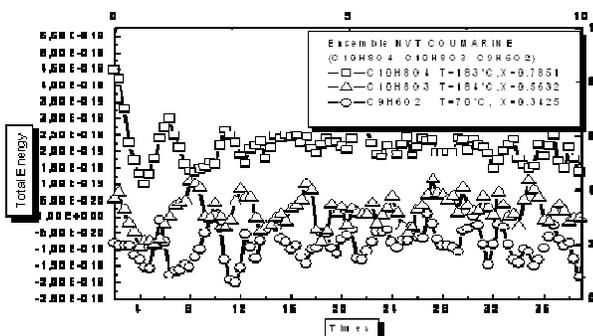


Figure 5: Evolution of total energy in NVT ensemble.

Isothermal-isobaric system (NPT)

Structural Properties

The radial distribution functions of coumarins in NPT ensemble at the point Sp1 are reported in figure 6.

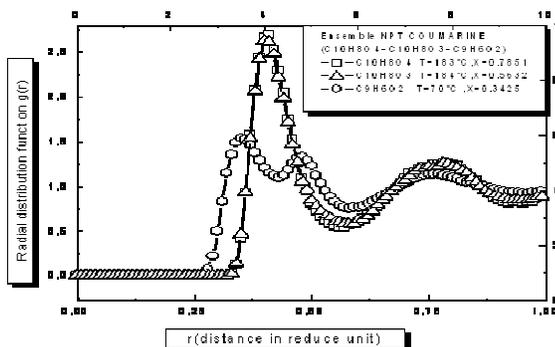


Figure 6 : Radial distribution functions of coumarins in NPT ensemble at the point Sp1.

From this figure, we can observe the existence of two maximum of each curve of coumarin. The substituted coumarins give comparable curves. Consequently, pressure and temperature are maintained constants during the simulation and the system is more stable than in NVT experience. As a result, radial distribution functions provide precise and good results.

Thermodynamic Properties

We have realised our calculations at the point Sp1. The thermodynamic properties (U , H) are calculated from the related references [36]. All our results are given in table 2.

We have found for the coumarin system that the energy of configuration U , and the enthalpy H are different for both NVT and NPT calculations. The temperature and the pressure remain fixed in the isothermal-isobaric system. An rising in temperature allows the energy of configuration and the enthalpy H to the large values. It shows, That ensemble gives very precise results for NPT comparing to NVT system (figure 7). We conclude that at any moment the energy of configuration is controlled in the time.

Compound	U (J/Mol)	H (J/Mol)	T (K)
C ₉ H ₆ O ₂	0.0324	2.4250	290.64
C ₁₀ H ₈ O ₃	0.0764	3.5862	285.63
C ₁₀ H ₈ O ₄	0.1204	5.8652	287.05

Table 2 : Calculated thermodynamic properties of coumarins at the point Sp1.

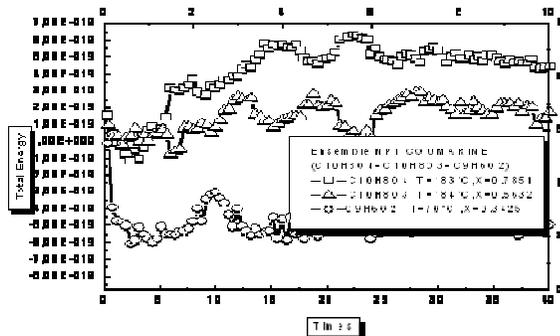


Figure 7 : Evolution of total energy in NPT ensemble.

In figure 8, the variation of volume is progressive for the C₁₀H₈O₃ coumarin. However, the curve reaches two maximum then stabilises for the second isomer. As result, the intermolecular sphere-sphere interactions of the first molecule increase and become significant in the time.

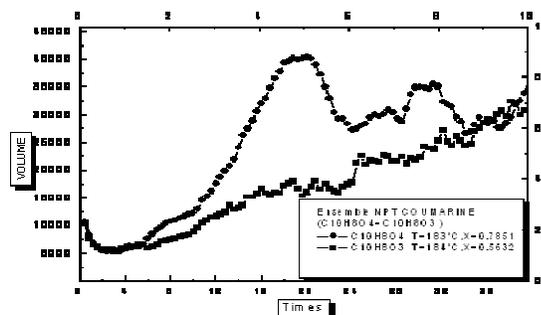


Figure 8 : Volume variation of coumarins in NPT ensemble.

COMPARATIVE STUDIES

Simulation calculations with the spectroscopic analysis

The proton chemical shift values reported in Table 3 show that the Δ value of the H₅ proton is the big one (+0.13). This Δ variation is due to anisotropic effect of aromatic cycle. The lowest one is -0.33 for H₃ proton due to attractor effect of carbonyl group. The big difference (+0.79) is observed for CH₃ because of its sp³ hybridizing. The estimated δ values were calculated using the CS ChemDraw software.

Some primary calculated harmonic frequencies are listed in Table 4 and compared with the experimental data. The descriptions concerning the assignment have also been indicated in the Table 6. The DFT Calculations with a hybrid functional B3LYP were performed with the Gaussian 03 software package using the Bery method [38] and were used to assign the calculated harmonic frequencies. Vibrational frequencies calculated at the B3LYP/6- 311G** level were scaled by the typical factor 0.96.

As seen from Table 4, the predicted harmonic vibration frequencies and the experimental data are different to each other. The biggest error occurs at C=O stretching vibration, with the biggest deviation being +124 cm⁻¹. In general, the calculated frequencies of the DFT calculation are confirmed the corresponding FT-IR vibration data and on the whole the DFTB3LYP/ 6-311G** level can predict the vibrational frequencies for the studied coumarins.

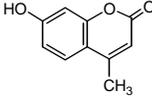
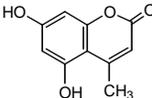
Compound	RMN ¹ H (δ ppm) (Experimental)	RMN ¹ H (δ ppm) (estimated)	Δ (ppm)
	A 300 MHz (DMSO-d ₆):		
	10.56 [s, 1H, OH];		
	7.59 [d, 1H, JHH = 8.6 Hz, H5];	7.46 [1H, H5];	+0.13
	6.80 [dd, 1H, JHH = 8.6 Hz, H6];	6.69 [1H, H6];	+0.11
	6.70 [d, 1H, JHH = 8.6 Hz, H8];		
	6.12 [s, 1H, H3];	6.67 [1H, H8];	+0.03
	2.36 [s, 3H, CH ₃] ²² .	6.23 [1H, H3];	-0.11
	A 400 MHz (Acétone-d ₆):		
	9.50 [s, 1H, OH];	1.71 [3H, CH ₃].	+0.65
	7.59 [d, 1H, JHH = 8.6 Hz, H5];		
	6.84 [dd, 1H, JHH = 8.6 Hz, 2.3 Hz, H6];	7.46 [1H, H5];	+0.13
	6.72 [d, 1H, JHH = 2.3 Hz, H8];	6.69 [1H, H6];	+0.15
6.06 [s, 1H, H3];	6.67 [1H, H8];	+0.05	
2.41 [s, 3H, CH ₃] ³⁷ .	6.23 [1H, H3];	-0.17	
	1.71 [3H, CH ₃].	+0.70	
	A 200 MHz (DMSO-d ₆):		
	10.5 [s, 1H, OH, H7];		
	10.3 [s, 1H, OH, H5];		
	6.30 [s, 1H, H8];	6.23 [1H, H8];	+0.07
	6.20 [s, 1H, H6];	6.16 [1H, H6];	+0.04
	5.90 [s, 1H, H3];	6.23 [1H, H3];	-0.33
	2.50 [s, 3H, CH ₃] ¹⁹ .	1.71 [3H, CH ₃].	+0.79
	Δ (ppm) = δ(¹ H experimental) - δ(¹ H estimated).		

Table 3: Proton chemical shifts of coumarins.

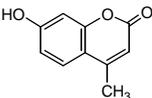
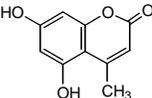
Compound	Exp-IR (νcm ⁻¹) (with KBr)	Calculated (νcm ⁻¹) (B3LYP/6-311G**))	∇(cm ⁻¹)
	3013(Ar-H) str.	3125(Ar-H)	-112
	2858(CH ₃) str.	2768(CH ₃)	+90
	1679(C=O) str.	1670(C=O);	+09
	1068(C-O) bend ²² .	1015(C-O)	+53
	3119 (Ar-H) str.	3042(Ar-H),	+77
	3500 (OH) str.	3450 (OH),	+50
	2816(CH ₃) str.	2789(CH ₃),	+27
1670 (C=O) str.	1670 (C=O),	00	
1075(C-O) bend ³⁷ .	1175(C-O)	+100	
	3159 (O-H) str.	3245 (O-H),	-86
	1670 (C=O) str ¹⁹ .	1546 (C=O)	+124
∇(cm ⁻¹) = Exp-IR (cm ⁻¹) - Calculated (νcm ⁻¹)			

Table 4: Comparison of observed and calculated vibrational spectra of coumarins.

Thermodynamic properties of coumarins

Using the MD simulation approach, we have studied the evolution thermodynamic properties of coumarins in NVT and NPT ensembles. The calculated values in reduced unit are reported in table 5 [39].

We observe that the energy of configuration U* changes with the raise of the temperature. This energy is more significant in NPT ensemble because of its stability than in the NVT one. For the C₁₀H₈O₄ isomer, The energy U* is very important (substituted molecule). The situation is reversed for the enthalpy H*. The



pressure is irregular and varied with temperature. Its value increases with the substituted factor and becomes important for the NVT system (table 5).

DMLJ	U*	H*	P*
NVT C ₁₀ H ₈ O ₄	-0.0687±0.00726	<u>-0.0178±0.0001</u>	0.4256±1.5845
NVT C ₁₀ H ₈ O ₃	-0.2546±0.12560	-0.3560±0.1356	0.2536±1.2360
NVT C ₉ H ₆ O ₂	-0.1526±0.14256	-0.2563±0.1526	0.1250±1.2156
NPT C ₁₀ H ₈ O ₄	-0.0452±0.1236	<u>-0.0562±0.0256</u>	0.3256±1.52365
NPT C ₁₀ H ₈ O ₃	-0.1986±0.1522	-0.2458±0.0524	0.1560±1.12450
NPT C ₉ H ₆ O ₂	-0.0526±0.0256	-0.1562±0.2540	0.0255±1.14520

Table 5: Calculated thermodynamic properties in NVT and NPT ensembles.

CONCLUSION

In this work, we have studied the evolution of thermodynamic and structural properties for 7-hydroxy-4-methyl coumarin and 5,7-dihydroxy-4-methyl coumarin. We have used the Lennard-Jones potential model in the molecular dynamics simulation. We have chosen the MD method to predict much better the characteristics. This method provides an advantage to confirm the structure-activity relationship for these compounds. We have calculated the thermodynamic and structural properties for both the NVT and NPT ensembles of hydroxy derivatives of 4-methyl coumarin.

We conclude that our simulation model in NPT system gives precise results and approaches very well the experimental data. We hope to use this model to study the properties of coumarin in appropriate solvent.

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