Quantum chemical insight and continuum solvation prediction of halogen substituted isoxazol 5-yl methanol compounds by PCM method using density functional theory

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Abstract
The polarizable continuum model (PCM) is employed to investigate theoretically the solvation of three heterocyclic compounds containing halogens. The PCM analysis has been carried out for (3-(4-Bromophenyl) isoxazol-5-yl) methanol, (3-(3- fluorophenyl) isoxazol-5-yl) methanol and (3-(3-Chlorophenyl) isoxazol-5-yl) methanol in ten solvents with wide range of dielectric constants. In this paper, we report the results obtained in the computation of electrostatic interaction, repulsive component of Gibb's free energy of solvation, cavitation enthalpy and entropy of solvation for the three isoxazols in various solvents. The induced dipole moments of these three isoxazols are also calculated in these solvents. The thermodynamic properties of the systems, such as free energies, electrostatic interaction, cavitation enthalpy and dipole moment are discussed in terms of the physical properties such as dielectric constant, index of refraction, surface tension and molecular size of the solvents.

Keywords: solvation, electrostatic, free energy, cavitation

1. Introduction
1.1 Rationale: Isoxazole is a five membered heterocyclic compound containing oxygen and nitrogen atoms in the [1, 2] positions, its partially saturated analogs are called isoxazolines and completely saturated analog is isoxazolidine. Isoxazole is an azole with an oxygen atom next to the nitrogen. Isoxazoles are an important class of heterocycles, which are largely employed in the area of pharmaceuticals and therapeutics such as insecticidal, antibacterial, antibiotic, antitumour, antifungal, antituberculosis, anticancer and ulcerogenic. Isoxazole derivatives are used in the market as COX-2 inhibitor and anti-inflammatory drugs. Isoxazole derivatives such as sulfamethoxazole, sulfisoxazole, oxacillin, cycloserine and acivicin have been in commercial use for many years [1-5]. They isolated a liquid base by heating nitroethane with aqueous alkalies to obtain [3, 4, 5] -trimethylisoxazole. A very significant contribution to the development of isoxazole chemistry came between 1930–1946 from Quilico's studies on the synthesis of ring system from nitrile oxides and unsaturated compounds [6]. The most fundamental thermodynamic quality characterizing solubility is the free energy of salvation [7]. In order to understand the factors affecting the solubility of the two thiazole amines in solvents of different polarities the free energy of solution of these compounds and their components are computed and correlated with the physical properties of the solvents. The calculation of free energies and cavitation enthalpies is performed with conductor like polarizable continuum model (C-PCM).

2. Procedure
2.1 Materials and Methods of computation
The molecular geometries of (3-(4-Bromophenyl) isoxazol-5-yl) methanol, (3-(3- fluorophenyl) isoxazol-5-yl) methanol and (3-(3-Chlorophenyl) isoxazol-5-yl) methanol are optimized and the optimized geometries are solvated with the solvent of various ranges of dielectric constant. Computation has been performed both in the gas phase and in the solvent medium using polarizable continuum model (PCM) by the B3LYP method with 6-311++G (d, p) basis set to interpret the solvent effect on the behavior of the solute molecules. The computer program GAUSSIAN 03 was used for this purpose [8]. The optimized structure of the isoxazol compounds used in the present investigation is depicted in Fig. 1. Solvation analysis is done using wide range of solvents to interrupt the solvation effect of the molecules. The solvents selected are water, methanol, chloroform, toluene, benzene, and carbontetrachloride. These solvent exhibits a broad range of characteristics indicated in Table 1. In the correlation of free energy of solution and dispersive interaction energy, we used the polarizability function [F(ε)] which is a function of dielectric constant and these values are calculated using the Clausius–Mossotti equation

$$F(\varepsilon) = \{\varepsilon\text{-}1/ \varepsilon\text{+}2\} (M/\rho) \text{ ------------ (1)}$$

Where, ε= dielectric constant, M = molar mass and ρ=density of solvents.

3. Data, Value and Validation

The standard state free energy of solvation is the free energy difference associated with the transfer of a solute from gas phase to a given solvent and it is a fundamental quantity that describes the interaction between a solute molecule and the solvent in which it is dissolved [9-11]. The solvation analysis and free energy of solution data of important complex solutes in different solvents are useful synthetic organic chemists as well as biochemist. The solvations of halogenated isoxazol are investigated. For this purpose the free energy, electrostatic interaction, dispersive energy and repulsion energy are calculated by PCM method. The induced dipole moment and cavitation enthalpies are also calculated.

3.1 Electrostatic energy

Table 2 contains the electrostatic interaction energies of three halogenated isoxazol derivatives. It may point out that the electrostatic interaction energy values are less in non-polar solvents and in large in more polar solvents. Generally the electrostatic energy of the solute molecules increases with increasing the dielectric constant of the medium. The electrostatic interaction energy increases from CCl_4 to water except CH_3NO_2. This may be due to the reduced bond acidity and least polar activity between solvent and solute molecules which is balanced with solvent-solute dispersive interactions. In the present study, water provides more negative electrostatic interaction energy than by other solvents, due to the high dielectric constant of the water. This higher dielectric constant provides more macroscopic surface tension for the polarizability of inter molecular hydrogen bond formation. The plots of dielectric constant Vs electrostatic interactions in different solvent for the three solute molecules depicted in fig. 2.

The electrostatic energy of bromo, fluro, chloro derivatives in the given solvents are compared and it is observed that the fluro compound has higher electro static interaction than the other two compounds due to more electronegativity of fluorine.

3.2 Dispersion energy

The dispersion energy is the electronic polarization energy from mutual polarization of the solute and solvent [12]. This polarization, in turn, may depend on the refractive index and dipole moment of the solvent molecule. It is evident from the table that the dispersion energy is more negative for the three solutes in toluene and benzene among other organic solvents, which has small diploe moments. This may be due to higher quadruple moments of benzene and toluene. In table 3 we observed that the dispersion energy is less for bromo isoxazol than that of chloro and fluro isoxazol compounds. This may be due to the larger polarizability and size of bromine atom. Fig.3 represents the plot of dispersive energy against polarizabiltiy function $F(\varepsilon)$. The overlapping curves indicate that the dispersion energy is not influenced by the structural variation in solute. The negative value of the dispersion energy increases with increase in $F(\varepsilon)$ value and in alcoholic and chlorine solvents, the derivation is observed.

3.3 Repulsive energy

The repulsive energy is important parameters to be considered in solvation analysis. Table 4 provides the computed values of repulsive energies for the three solute molecules in different media. In all the solvents we observed the positive repulsive energies due to the solute- solute interactions. The more positive value of all the three compounds in benzene and toluene solutions is due to the fact that the three solute and aromatic hydrocarbon solvents contain π electrons and there may be repulsive force between them. It may be pointed out that the repulsive energy is high in toluene and benzene for the three solutes suggesting that these solutes may influence the solubility properties of the investigated solutes in aromatic hydrocarbons.

The repulsive energy can be correlated with the refractive index of the solvent. It is known that the repulsive energy generally increases with decrease in refractive index of the solvent and it is shown in Fig. 4.

3.4 Free Energy

Table 5 shows how the different characteristics of each solvent affect the free energy of salvation of the three selected solute molecules. By comparing the free energies of the molecules, the non polar solvent provide more favourable than that of the free energies in polar solvent except CCl_4. Since, the macroscopic surface tension of a particular solvent represents the energy required to make a surface in the solvent. For the solvent acetone, the refractive index is smaller than those of benzene and toluene. In addition, the hydrogen bond basicity parameter for acetone is larger than that of benzene and toluene. These two factors result in the free energies of solvation in solute molecules with acetone than benzene and toluene. The free energies of the three solute molecules in solvents Toluene, Benzene and CCl_4 are least favourable out of those all the solvent listed which is reflected from Fig.5. Plots of free energy against dielectric constant are given in Fig.6. These plots show that the influence of dielectric constant on free energy is significant in organic solvents and the free energy values are more negative in organic solvents with higher dielectric constant.

3.5 Cavitation energy

The cavitation free energy is an important contribution to the salvation of free energy. It is of basic importance in the usual partition that is based on different nature of solute–solvent interactions. In PCM, it is possible to calculate the fee energy difference between a molecule in gas phase and in a liquid solvent which is called cavitation energy. The cavitation energy will influence the solubility when it is more positive and will reduce the negative value of free energy of solution. The computed cavitation energy values for isoxasole compounds in different solvents by B3LYP method with 6-311++G(d,p) basis set are listed in Table 6. Among all the solvents, water provides the highest positive values for both molecules. Thus the solvation of halo ethynyl benzene in water is more endothermic than in other solvents in the present study.

3.6 Prediction of induced dipole moment

The prediction of induced dipole moments depends upon the electrostatic interaction that can be produced by additional adjustments of bond dipoles. The dipole moments are

computed for different combinations of solvent– solute and the values are summarized in Table 7-8. It is noticed that there is no that much variation of dipole moments of all the three solute molecules. However, in the case of (3-(3- fluorophenyl) isoxazol-5-yl) methanol there is a slight variation of the dipole moments. The changes in the dipole moments are studied based on the dielectric behavior of the solvent. Plots of induced dipole moment against dielectric constant are given in Fig.7.
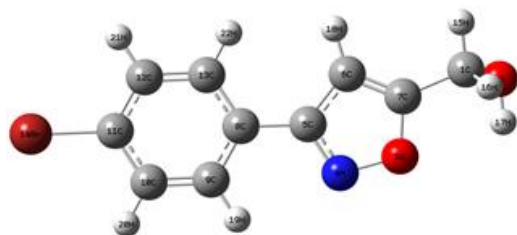
a. (3-(4-Bromophenyl) isoxazol-5-yl) methanol
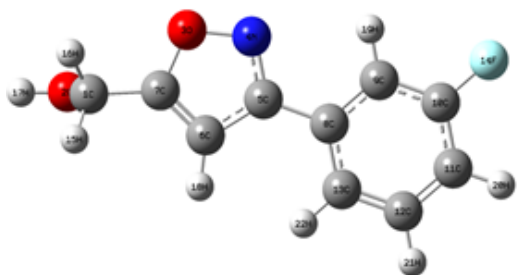
b. (3-(3-Fluorophenyl) isoxazol-5-yl) methanol

c. (3-(3-Chlorophenyl) isoxazol-5-yl) methanol

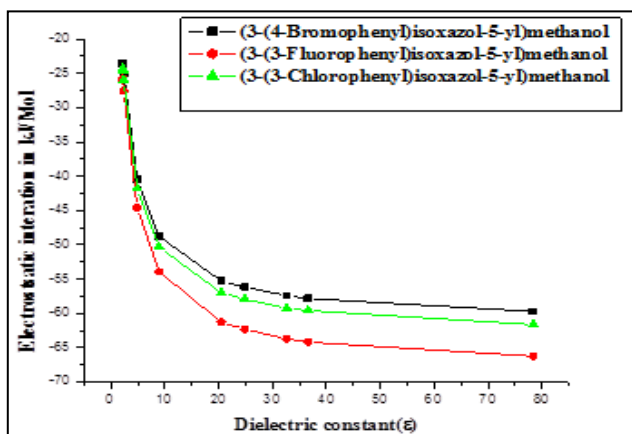**Fig 1:** Optimised structure of halogen substituted isoxazol -5-yl methanol derivatives

Fig 2: Schematic drawing of dielectric constant of various solvents studied here Vs corresponding electrostatic interaction energies
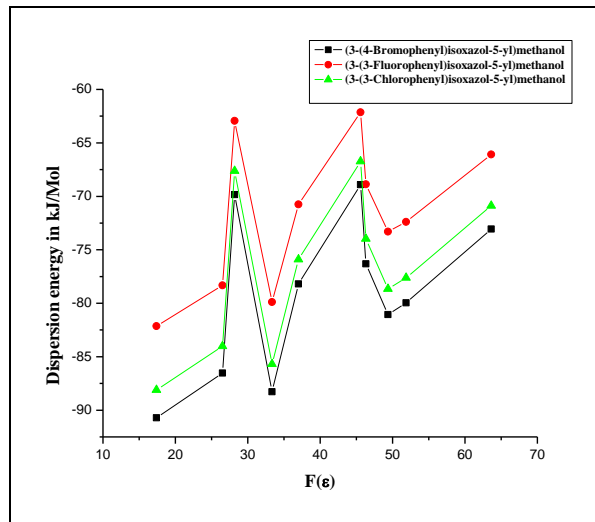

Fig 3: Schematic drawing of $F(\varepsilon)$ of various solvents studied here Vs corresponding dispersion energy
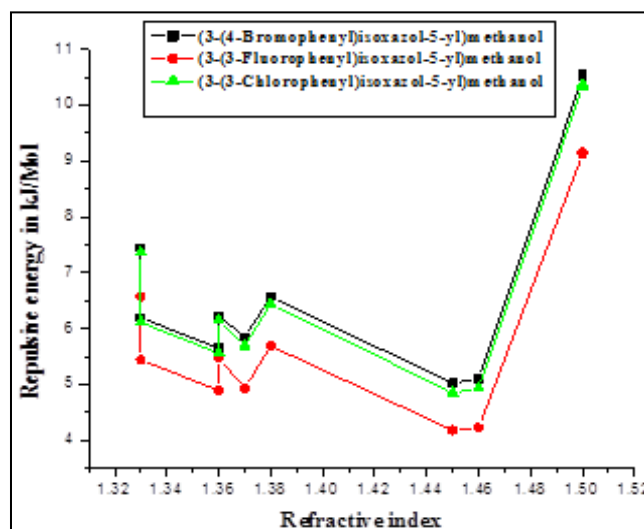

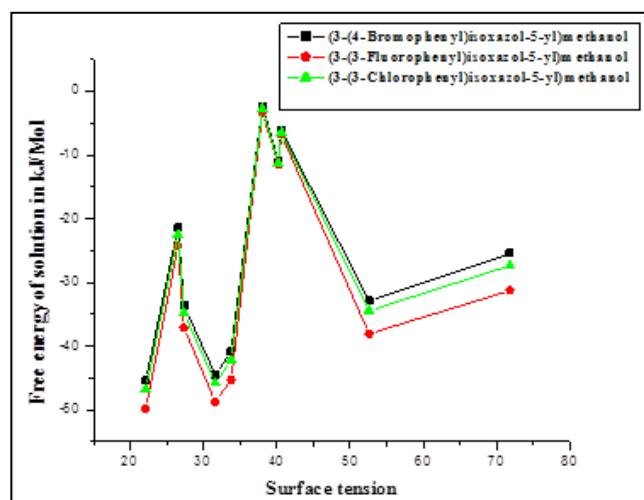**Fig 4:** Schematic drawing of refractive index of various solvents studied here Vs corresponding repulsive energies

Fig 5: Schematic drawing of surface tension of various solvents studied here vs corresponding Free energy of solution
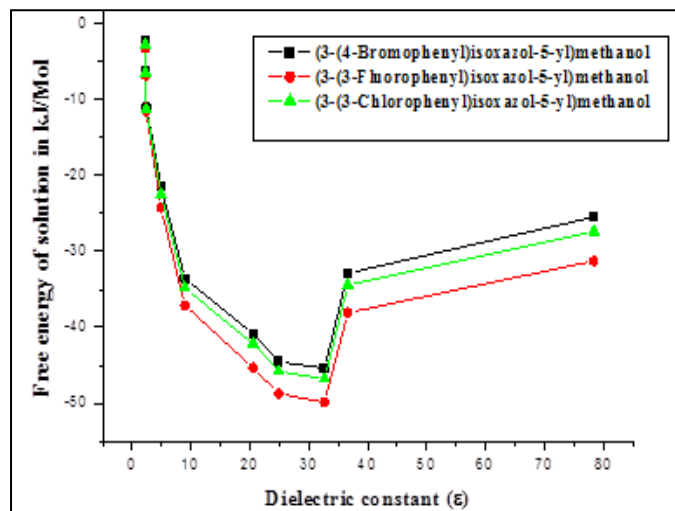
bond acidity, β — Abraham's hydrogen bond basicity. r —atomic radius, F(ε) —.Polarisability function.

Fig 6: Schematic drawing of dielectric constant of various solvents studied here Vs corresponding Free energy of solution
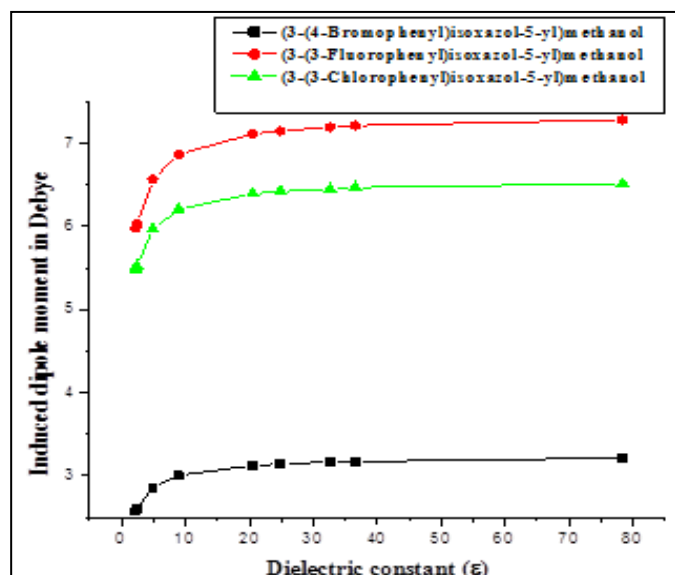

Fig 7: Schematic drawing of dielectric constant of various solvents studied here Vs corresponding Induced dipole moments of 5-substituted isoquinolines.

Table 1: Solvent descriptors

Solvent	ε	n	γ	α′	β	r	F(ε)
Water	78.35	1.33	71.81	0.82	0.35	2.77	17.38
Nitromethane	36.56	1.38	52.58	0.06	0.31	4.31	49.38
Methanol	32.63	1.33	22.12	0.43	0.47	3.71	37.00
Ethanol	24.85	1.36	31.62	0.37	0.48	4.7	51.87
Acetone	20.49	1.36	33.77	0.04	0.49	4.76	63.63
Dichloromethane	8.93	1.37	27.33	0.1	0.05	4.54	46.33
Chloroform	4.9	1.45	26.53	0.15	0.02	4.96	45.59
Toluene	2.37	1.5	40.2	0	0.14	5.64	33.36
Benzene	2.27	1.5	40.62	0	0.14	5.26	26.52
Carbontetrachloride	2.23	1.46	38.04	0	0	5.37	28.20

ε — dielectric constant at 298 K, n — index of refraction at optical frequencies at 298 K. $\gamma - \gamma_m / \gamma_o$; γ_m — macroscopic surface tension at a liquid–air interface. $\gamma_0 = 1$ cal/mol/A2. α′ — Abraham's hydrogen

Table 2: Electrostatic interaction energy of halogenated isoxazol kJ/Mol

Solvent	(3-(4-Bromophenyl) isoxazol- 5-yl) methanol	(3-(3-Fluorophenyl) isoxazol- 5-yl) methanol	(3-(3-Chlorophenyl) isoxazol- 5-yl) methanol
Water	-59.72	-66.24	-61.64
Nitromethane	-57.84	-64.19	-59.59
Methanol	-57.42	-63.73	-59.30
Ethanol	-56.16	-62.31	-57.92
Acetone	-55.29	-61.31	-57.00
Dichloromethane	-48.76	-53.91	-50.35
Chloroform	-40.48	-44.58	-41.82
Toluene	-25.18	-27.56	-26.01
Benzene	-23.75	-25.97	-24.55
Carbontetrachloride	-23.54	-25.72	-24.30

Table 3: Dispersion energy in of halogenated isoxazol kJ/Mol

Solvent	(3-(4-Bromophenyl) isoxazol- 5-yl) methanol	(3-(3-Fluorophenyl) isoxazol- 5-yl) methanol	(3-(3-Chlorophenyl) isoxazol- 5-yl) methanol
Water	-90.71	-82.13	-88.11
Nitromethane	-81.05	-73.31	-78.66
Methanol	-78.20	-70.76	-75.90
Ethanol	-79.96	-72.39	-77.62
Acetone	-73.06	-66.08	-70.88
Dichloromethane	-76.32	-68.88	-73.98
Chloroform	-68.92	-62.14	-66.74
Toluene	-88.28	-79.88	-85.69
Benzene	-86.53	-78.33	-84.02
Carbontetrachloride	-69.84	-62.94	-67.62

Table 4: Repulsion energy of halogenated isoxazol in kJ/Mol

Solvent	(3-(4-Bromophenyl) isoxazol- 5-yl) methanol	(3-(3-Fluorophenyl) isoxazol- 5-yl) methanol	(3-(3-Chlorophenyl) isoxazol- 5-yl) methanol
Water	7.44	6.57	7.36
Nitromethane	6.57	5.69	6.44
Methanol	6.19	5.44	6.11
Ethanol	6.23	5.48	6.15
Acetone	5.65	4.89	5.56
Dichloromethane	5.85	4.93	5.69
Chloroform	5.02	4.18	4.85
Toluene	10.54	9.16	10.37
Benzene	10.50	9.12	10.33
Carbontetrachloride	5.10	4.22	4.93

Table 5: Free energy of solution of halogenated isoxazol in kJ/mol

Solvent	(3-(4-Bromophenyl) isoxazol- 5-yl) methanol	(3-(3-Fluorophenyl) isoxazol- 5-yl) methanol	(3-(3-Chlorophenyl) isoxazol- 5-yl) methanol
Water	-25.468	-31.281	-27.392
Nitromethane	-32.871	-38.056	-34.418
Methanol	-45.375	-49.849	-46.797
Ethanol	-44.538	-48.720	-45.793
Acetone	-40.858	-45.291	-42.155
Dichloromethane	-33.581	-37.094	-34.794
Chloroform	-21.454	-24.297	-22.499
Toluene	-11.040	-11.542	-11.333
Benzene	-6.148	-6.858	-6.524
Carbontetrachloride	-2.342	-3.346	-2.802

Table 6: Cavitation energy of halogenated isoxazol of halogenated isoxazol in kJ/Mol

Solvent	(3-(4-Bromophenyl) isoxazol- 5-yl) methanol	(3-(3-Fluorophenyl) isoxazol- 5-yl) methanol	(3-(3-Chlorophenyl) isoxazol- 5-yl) methanol
Water	117.51	110.53	115.01
Nitromethane	99.45	93.76	97.40
Methanol	84.06	79.21	82.30
Ethanol	85.35	80.50	83.60
Acetone	81.84	77.20	80.17
Dichloromethane	85.65	80.75	83.85
Chloroform	82.93	78.25	81.21
Toluene	91.88	86.73	90.00
Benzene	93.63	88.32	91.71
Carbontetrachloride	85.94	81.09	84.18

Table 7: Dipole moment of halogenated isoxazol in Debye units.

(3-(4-Bromophenyl) isoxazol- 5-yl) methanol	(3-(3-Fluorophenyl) isoxazol- 5-yl) methanol	(3-(3-Chlorophenyl) isoxazol- 5-yl) methanol
2.2165	5.2059	4.7826

Table 8: Induced dipole moments of halogenated isoxazol in Debye

Solvent	(3-(4-Bromophenyl) isoxazol- 5-yl) methanol	(3-(3-Fluorophenyl) isoxazol- 5-yl) methanol	(3-(3-Chlorophenyl) isoxazol- 5-yl) methanol
Water	3.21	7.28	6.51
Nitromethane	3.17	7.21	6.47
Methanol	3.17	7.20	6.45
Ethanol	3.14	7.15	6.42
Acetone	3.12	7.11	6.40
Dichloromethane	3.00	6.87	6.21
Chloroform	2.86	6.57	5.97
Toluene	2.60	6.03	5.52
Benzene	2.58	5.98	5.48
Carbontetrachloride	2.57	5.98	5.47

4. Conclusion

The polarizable continuum model (PCM) is used to investigate the solvation of three isoxazol derivatives in ten solvents with a wide range of dielectric constants. We report the results obtained in the computation of electrostatic, dispersion and repulsive interaction components of Gibb's free energy of solvation along with cavitation energies for these systems.

The electrostatic interaction contribution to the free energy can be satisfactorily correlated with the dielectric constant of the solvent. Dispersion energy in all the systems is influenced by the polarizability of the solvent, which in turn depend upon its molecular size. There is a satisfactory correlation between the repulsion energy and refractive index of the solvent. The cavitation energy of the three isoxazol derivatives in different solvents can be correlated with the macroscopic surface tension of the solvent. The data for free energies of solution of three compounds in ten solvents indicate that the dissolution process is more favored in alcohols and nitromethane but less favorable in aromatic hydrocarbons and CCl$_4$. Induced dipole moments for the three isoxazol derivatives in ten chosen solvents are reported and discussed.

5. References

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