

Effect of Solvation on the Charge Distribution of a Series of Anionic, Neutral, and Cationic Species. A Quantum Molecular Similarity Study

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The changes in the charge distribution induced upon solvation for a series of small anionic, neutral, and cationic species have been analyzed. The effect of solvent polarization on the solute wave function has been introduced from high-level *ab initio* self-consistent reaction field calculations. Determination of quantum molecular similarity measures allows us to quantify the redistribution of the charge density and the changes in Coulombic repulsions under the effect of hydration and establish some general trends depending on the electronic nature of the species.

1. Introduction

The solvent effect is of paramount importance for thermodynamic and kinetic studies of chemical reactions.^{1,2} This effect, which is especially relevant for polar solvents, results in a redistribution of the electron density which, in turn, influences molecular reactivity. The theoretical representation of the mutual solute–solvent polarization requires the use of quantum mechanical methods.^{3,4} Among them, self-consistent reaction field (SCRF) methods^{3,5–13} have emerged as a good strategy for obtaining the wave function of the solute in solution, thus incorporating charge redistribution induced by the solvent. These methods treat the solvent as a continuum dielectric medium, which reacts against the solute charge distribution generating a reaction field, which is then added as a perturbation operator (V) to the solute Hamiltonian *in vacuo* (eq 1). Due to the dependence between the perturbation operator and the solute wave function, an iterative (SCRF) procedure is typically used.

$$(\hat{H}^{\circ} + \hat{V})\Phi = E\Phi \quad (1)$$

Since eq 1 provides the wave function of the solute in solution, comparison of the wave functions *in vacuo* and in solution enables the determination of the solvent polarization effect on the charge distribution of the solute, and accordingly of the change in molecular properties upon solvation.

A detailed knowledge of changes in the solute charge distribution is essential to understand the solvent influence on molecular reactivity. In this sense, recent studies have been focused on the effect of hydration on the shape, size, and anisotropies of several small prototypical anions,¹⁴ neutral molecules,¹⁵ and cations.¹⁶ In these studies attention was mainly paid to the changes in the electrostatic potential determined *in vacuo* and in aqueous solution in regions outside the van der Waals surface, and also to the critical points that characterize

the topography of the MEP.^{17–19} These studies provided indirect but useful information on solute charge redistribution upon solvation for molecules with the same net charge. Unfortunately, analysis of the magnitude and topography of the MEP is not so useful when molecules with different net charges are compared. In this case direct, quantitative measures of comparison of the electron distribution have to be used.

A quantitative analysis of the charge density redistribution can be achieved using quantum molecular similarity measures (QMSMs). These techniques are very useful in studies devoted to defining relationships between molecular structure and properties. A clear example is the application of similarity measures to the electrostatic potential within the framework of quantitative structure–activity relationships.^{20–22} A particular case is self-comparison of a molecule, i.e. the comparison of a molecule with itself. In this case, the similarity measure is a molecular descriptor that quantifies its particular electronic charge distribution.²³ Calculation of self-similarity indexes have proven useful to better understand how a series of simple chemical rearrangement reactions proceed along the reaction coordinate, through an analysis of changes in the charge density distribution of the molecular systems while proceeding from reactants to transition states to products.²⁴

From the above statements, it immediately follows that the QMSM technique can be a useful tool for studying the effect of an external perturbation on the charge distribution. In fact, the effect of applying a uniform electric field on the reaction coordinate of a model of a Walden inversion reaction has been reported.²⁵ In this study we extend the usefulness of the molecular similarity to analyze the influence of the solvent polarization on the charge distribution of the solute. By using different QMSM techniques, the charge redistribution induced upon solvation for neutral molecules, cations, and anions will be studied. The information provided by the QMSM techniques, combined with the analysis of the MEP^{14–16} and molecular volumes, allows us to gain insight into the general trends of the solvent effect.

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2. Methodology

The wave functions *in vacuo* for the anionic (NH_2^- , OH^- , CH_3NH^- , CH_3O^- , and SH^-), neutral (NH_3 , H_2O , CH_3NH_2 , CH_3OH , and SH_2), and cationic (NH_4^+ , H_3O^+ , CH_3NH_3^+ , CH_3OH_2^+ , and SH_3^+) species were computed at the *ab initio* SCF-RHF level using the 6-31++G(d) basis set.²⁵ An optimized *ab initio* version^{26,27} of the SCRf method developed by Miertus, Scrocco, and Tomasi (MST^{3,6,7}) using the same basis set was employed for calculations in aqueous solutions. In all cases, geometry optimizations were carried out *in vacuo* and the optimized geometry was then used for the computations in solution. This allowed for determination of the solvent effect on the electron distribution without interferences arising from nuclear rearrangements.

Exact QMSMs were estimated using eq 2, where $\Theta(\mathbf{r}_1, \mathbf{r}_2)$ is a positive operator that depends on two electron coordinates. Two different operators were used: the Dirac delta function, $\delta(\mathbf{r}_1 - \mathbf{r}_2)$, which gives an overlap-like similarity measure, and the operator $1/r_{12}$, which provides a Coulomb-like similarity measure. ρ_A and ρ_B are the charge density distributions of quantum objects A and B, respectively. For a given molecule ($A = B$) in a particular environment, eq 2 represents the so-called quantum molecular self-similarity measure (self-QMSM), Z_{AA} . From a quantum mechanical point of view, the overlap-like self-QMSM can be viewed as the expectation value of the density operator and measures the increase in concentration of the molecular electron density distribution. Likewise, the Coulomb-like self-QMSM is the expectation value corresponding to the electronic term of the MEP and reflects the Coulombic repulsion in a particular density distribution given that it contributes the classical part of the electron–electron repulsion.

$$Z_{AB}(\Theta) = \int \int \rho_A(\mathbf{r}_1) \Theta(\mathbf{r}_1, \mathbf{r}_2) \rho_B(\mathbf{r}_2) d\mathbf{r}_1 d\mathbf{r}_2 \quad (2)$$

Once the similarity measure has been defined, an Euclidean distance²⁸ between the charge density distributions of A and B can be defined (see eq 3) in such a way that two objects completely similar have a distance of 0 between them, and the distance increases as the similarity between the two electron distributions is reduced. For a complete review on the foundations of quantum molecular similarity and recent developments in applications, see ref 29.

$$d_{AB} = \sqrt{Z_{AA} + Z_{BB} - 2Z_{AB}} \quad (3)$$

QMSM analyses were complemented with the inspection of the MEP in regions outside the van der Waals surface. Specifically, MEPs in the gas phase and in aqueous solutions were determined in layers placed between 1.0 and 2.0 times the van der Waals radii of atoms.^{14–16} Finally, molecular volumes in the gas phase and solution were determined according to Bader's analysis³⁰ using an electron density of 0.001 au for integration.

SCF and SCRf calculations were performed using a modified version of the MonsterGauss computer program.³¹ QMSMs were calculated by means of the Messem program.³² Molecular electrostatic potentials were computed with the MOPETE/MOPFIT programs.³³ Molecular volumes were determined using the PROAIM package.³⁰ All the computations were carried out on the Cray YMP computer of the Centre de Supercomputació de Catalunya (CESCA) and on workstations in our laboratories.

3. Results and Discussion

Tables 1 and 2 show, respectively, the overlap-like and Coulomb-like self-QMSM values corresponding to the charge

TABLE 1: Overlap-like Quantum Molecular Self-Similarity Measures (in au), Distance (in au), and Molecular Volumes (in cm³/mol) for the Anionic, Neutral, and Cationic Species Studied

species	overlap-like self-QMSM			volume	
	<i>in vacuo</i>	solution	distance	<i>in vacuo</i>	solution
NH_2^-	52.250 44	52.234 51	0.019 77	27.96	25.44
OH^-	80.836 66	80.841 89	0.014 25	21.01	20.02
CH_3NH^-	83.863 64	83.840 89	0.032 71	41.11	39.44
CH_3O^-	112.474 78	112.464 34	0.028 28	35.89	34.32
SH^-	814.756 87	814.845 02	0.035 64	37.48	34.48
NH_3	52.341 65	52.326 21	0.014 25	20.83	20.85
H_2O	80.972 19	80.942 40	0.018 68	16.29	16.20
CH_3NH_2	83.960 55	83.949 18	0.013 93	35.01	35.05
CH_3OH	112.605 98	112.585 60	0.015 49	31.15	30.87
H_2S	814.985 26	814.961 65	0.012 25	29.64	29.75
NH_4^+	52.380 33	52.377 02	0.003 16	17.72	17.86
H_3O^+	80.910 18	80.905 18	0.012 04	14.45	14.46
CH_3NH_3^+	84.039 51	84.016 06	0.016 09	31.99	32.32
CH_3OH_2^+	112.607 32	112.582 57	0.017 61	29.05	29.24
H_3S^+	815.072 83	815.038 17	0.010 00	25.68	25.99

TABLE 2: Coulomb-like Quantum Molecular Self-Similarity Measures (in au), Distance (in au) and Range of MEP rms Deviations at the Layers between 1.0 and 2.0 Times the van der Waals Radii of the Atoms for the Anionic, Neutral, and Cationic Species Studied

species	Coulomb-like self-QMSM			
	<i>in vacuo</i>	solution	distance	rms ^a
NH_2^-	75.225 25	75.948 86	0.066 29	8.38–1.60
OH^-	90.884 77	91.469 62	0.044 29	4.89–0.46
CH_3NH^-	172.510 82	173.405 99	0.095 24	9.77–4.40
CH_3O^-	191.286 98	192.327 88	0.082 10	8.34–3.77
SH^-	378.088 29	379.095 69	0.097 26	13.56–4.62
NH_3	78.244 64	78.290 69	0.032 08	3.67–1.19
H_2O	93.412 47	93.499 99	0.034 93	4.35–1.38
CH_3NH_2	175.772 55	175.816 82	0.032 71	3.49–1.30
CH_3OH	193.186 54	193.304 25	0.031 78	3.83–1.42
SH_2	381.438 82	381.550 69	0.032 09	3.22–1.21
NH_4^+	79.560 26	79.493 30	0.005 48	0.28–0.01
H_3O^+	94.472 77	94.467 73	0.023 58	2.90–0.93
CH_3NH_3^+	176.398 34	176.136 41	0.035 07	4.14–1.73
CH_3OH_2^+	192.183 73	192.002 98	0.035 64	3.90–1.55
H_3S^+	382.866 60	382.819 89	0.026 27	3.22–1.07

^a Data taken from refs 14 (anions), 15 (neutral), and 16 (cations). Values not reported in these references were computed in this study.

density distributions *in vacuo* and in solution. The Euclidean distance between the two charge distributions has been computed from the QMSM values (eq 3). The similarity values are compared with the changes in the molecular volume and in the electrostatic potential, since these widely used parameters provide an alternative insight into the charge redistribution. Thus, Table 1 reports the molecular volumes *in vacuo* and in solution, as determined from Bader's analysis (see Methods), and Table 2 gives the range of the root mean square (rms) deviation for the MEP determined in layers placed between 1.0 and 2.0 times the van der Waals radii of the atoms (see Methods). In the following sections these results will be discussed for each series of molecules (anionic, neutral, cationic), as well as for series of isoelectronic molecules.

A. Anionic Species. Inspection of Tables 1 and 2 demonstrates the complexity of the solvent effect on the electron distribution of solutes and the need to use several tests to obtain a complete picture of such effects. Comparison of molecular volumes in the gas phase and in solution (Table 1) demonstrates that solvation leads to a notable shrinking in molecular volume, which is due to the movement of outer electrons to regions closer

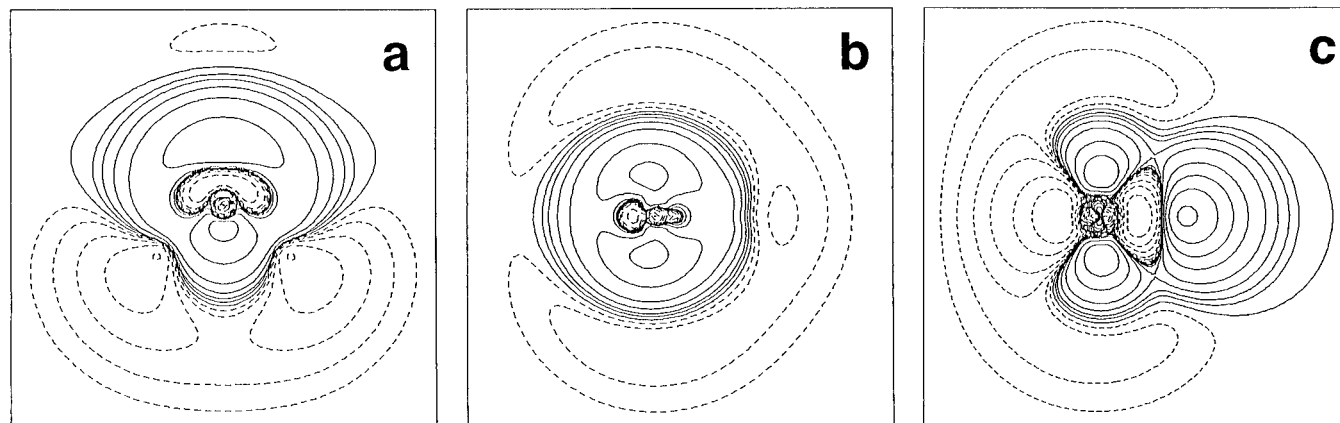


Figure 1. Difference maps between charge density distributions in solution and *in vacuo* for NH_2^- (a), OH^- (b), and SH^- (c). Heteroatoms are always located at the center of each picture. The solid line represents an increase in charge density upon solvation, the dotted line a decrease.

to the molecule.¹⁴ This concentration of charge is expected to increase the solute–solvent interaction, leading to better solvation.

Coulomb-like self-QMSM values reveal an increase in the Coulombic repulsion, as shown by the larger value of the self-QMSM value in solution (Table 2). This is in agreement with the compression of the molecular volume. Indeed, the ordering defined by the overlap-like and Coulomb-like Euclidean distances qualitatively reflects the range of the rms deviations in the MEP.¹⁴ In summary, Bader's molecular volumes, MEPs, and Coulombic-like self-QMSMs agree in the effect played by the solvent on the charge distribution of anions, which experiences a notable reduction in molecular volume due to the contraction of the electron distribution.

Inspection of the overlap-like QMSM values provides complementary and somewhat surprising information. Thus, in contrast to the MEPs, volume, and Coulombic-like self-QMSM parameters, no general trend is found when the overlap-like QMSM values are examined. Smaller values are obtained for NH_2^- , CH_3NH^- , and CH_3OH^- upon solvation, while the reverse trend is observed for OH^- and SH^- . The interpretation of these results is straightforward: the solvent leads to a dispersion of the electron distribution for NH_2^- , CH_3NH^- , and CH_3OH^- , while for OH^- and SH^- the electron density becomes more concentrated upon solvation.

The concentration of electron density upon solvation found for OH^- and SH^- agrees with the results obtained using Bader's analysis and Coulomb-like QMSM calculations. On the contrary, the dispersion of the electron density for NH_2^- , CH_3NH^- , and CH_3OH^- is surprising, since it apparently suggests a movement of the electron distribution to outer regions upon solvation. Inspection of the difference maps between the charge densities *in vacuo* and in solution (see Figure 1) for NH_2^- , OH^- , and SH^- shows that there is no inconsistency between the different parameters. Thus, the difference map for NH_2^- (Figure 1a) shows that the contraction of the molecular volume is not related to a concentration of the charge density near the nuclei. In fact, the charge density decreases around the nitrogen nucleus, while it is increased in the region of the lone pair and in the N–H bonds. This density rearrangement diminishes the self-QMSM value, even though the volume is reduced. For OH^- (Figure 1b) the charge density is accumulated nearly spherically around the oxygen nucleus. This explains the increase in the overlap-like similarity measure. Finally, for SH^- (Figure 1c) the charge density is scattered in regions near the sulfur nucleus pointing toward the hydrogen, but it is concentrated in regions perpendicular to the bond.

In summary, the solvent leads to an important shrinking on the molecular volume, owing to the movement of electrons to inner regions. However, the exact placement of this *extra* electron density is greatly modulated by the solute. The results show that in some cases the *extra* electron density is not accumulated around the nuclei (the regions of largest effect in the calculation of overlap-like QMSM values) but is concentrated in intermediate regions.

Comparison of the five anions reveals that Euclidean distances derived from QMSM values (overlap and Coulombic) agree in the following ordering of susceptibility to the solvent polarization: $\text{SH}^- > \text{CH}_3\text{NH}^- > \text{CH}_3\text{O}^- > \text{NH}_2^- > \text{OH}^-$. The same ordering is found for the MEP, but inspection of the molecular volumes leads to a slightly different ordering: $\text{SH}^- > \text{NH}_2^- > \text{CH}_3\text{NH}^- > \text{CH}_3\text{O}^- > \text{OH}^-$. These results demonstrate once again the complexity of the solvent effect on anions and the difficulty of defining such an effect in simple terms such as solute polarizability.

B. Neutral Species. The overlap-like self-QMSM *in vacuo* is always larger than in solution, which means that the charge distribution is scattered upon solvation. This agrees with findings reported previously,^{15,34} which showed that for polar neutral molecules the solvent promotes a charge redistribution that tends to increase the polarity, so that the interaction of the solute with the solvent molecules becomes more favorable. In this redistribution the electron density around the nuclei, especially the acidic hydrogens, is moved to outer regions around the most electronegative atom. This electron density rearrangement, nevertheless, has little effect on the molecular volume, which experiences a very small change upon solvation, but leads to large variations in the molecular dipole, as shown previously from SCRf and mixed MC-QM/MM calculations.³⁴

Coulomb-like QMSM values indicate an increase of the Coulombic repulsion upon solvation, as revealed by the smaller values *in vacuo* than in solution. This likely stems from the accumulation of electron density in regions near the electronegative atom, mainly in the regions of the lone pairs. However, this increase is moderate and amounts to 0.03–0.09%, which is 1 order of magnitude lower than that found for anions. The different magnitude of the solvent effect for anions and neutral molecules is also reflected in the overlap-like and Coulomb-like Euclidean distances. Thus, the distances range from 0.012 to 0.018 (overlap) and from 0.032 to 0.035 (Coulomb) for neutral molecules, whereas the variation for anions is 0.014–0.036 and 0.044–0.097, respectively. This also agrees with the smaller values of the rms error found for neutral molecules when compared with those for anions (see Table 2). All these

results agree with the fact that the molecular volume remains nearly unaffected upon solvation.

The behavior of the different neutral solutes prohibits a well-defined ranking of susceptibility to the solvent polarizing effect. The changes in the MEP, volumes, and QMSM measures are generally the same for the different solutes. This finding agrees with previous calculations^{15,34} that revealed a constant percentual increase in the molecular dipole induced by the solvent.

In summary, present results and those reported in previous studies^{15,34} show that the solvent induces a significant rearrangement of the solute charge distribution. This rearrangement shifts electron density from the neighborhood of the electro-positive atoms to the vicinities of the electronegative ones, resulting in an increase in the molecular dipole. Such a rearrangement enriches the electron density in the lone pairs, but the region near the nuclei remains almost unaltered, as noted by the overlap-like QMSM results. Furthermore, the differences in the volumes do not indicate a large transfer of electrons in the outer regions. The electron rearrangement mainly affects the electron density in intermediate regions, at a similar distance from the nuclei.

C. Cationic Species. The overlap-like self-QMSM values are larger *in vacuo* than in solution, which indicates a dispersion of the charge density, and a small expansion of the molecular volume is observed. These two findings can be rationalized as resulting from a shift of electron density toward regions far from the nuclei. Such a shift increases the positive charge density of the solute, which then stabilizes the cation-solvent interactions.¹⁶ This effect is also clearly supported by the Coulomb-like QMSM results, which indicate the expected decrease in the Coulombic repulsion interactions, as shown by the larger self-similarity values obtained *in vacuo*.

The analysis of the volumes, MEPs, and QMSM demonstrates that the solvent-induced changes in the charge distribution of cations is moderate, not too different in general from that found for neutral molecules. However, a detailed inspection of the parameters shows relevant differences in the solvent effect between neutral molecules and cations. Thus, while for neutral molecules the shift of electron density occurs, on average, in regions located at the same distance from the nuclei, for cations the electron movement from inner to outer regions is clearly observed.

The ordering given by the overlap-like and Coulomb-like distances and by the MEP rms is nearly the same. Thus, the methyl derivatives show the largest distances and rms deviations, suggesting a larger susceptibility to the solvent polarizing effect. The smallest susceptibility is found for NH_4^+ , which can be attributed to the tetrahedral structure of the ammonium cation. Finally, there is not a clear ordering of susceptibility to the solvent polarization for H_3O^+ and H_3S^+ . The Coulomb-like QMSM, MEP rms, and volume measures suggest that H_3S^+ is more susceptible, but the overlap-like QMSM values indicate larger changes for H_3O^+ .

In summary, water has a significant and quite specific effect on cations, which results in a small but significant shift of electrons from inner to outer regions. This shift leads to a moderate increase in the molecular volume and to an increase of the positive charge density in regions close to the nuclei.

D. Isoelectronic Series. The series of anionic, neutral, and cationic species can be viewed, in fact, as five isoelectronic series, each formed by an anion, a neutral molecule, and a cation. In the isoelectronic series, the first remarkable trend is the systematic decrease of the molecular volume when going from the anion to the cation, which agrees with chemical intuition. The largest changes of volume (both in absolute and relative

terms) are found for anions. For the series NH_3 , H_2S , and CH_3NH_2 the rank of solvent-induced perturbation in the volume is anion > cation > neutral, while for the oxygen-based series the order is anion > neutral > cation. Comparison of molecules with and without the methyl group shows that this group favors the change of volume for neutral molecules and cations, but for anions the situation is less clear, since it favors the perturbation for the oxygen-based series, while the reverse effect is found for the nitrogen-based series.

As noted before, changes in the volume are not always related to a concentration of charge density in the nuclear regions. Thus, for the series NH_3 , H_2S , and CH_3NH_2 the overlap-like QMSM values agree with the volume variation, but for H_2O and CH_3OH the overlap-like QMSM values of cations are smaller than those of neutral molecules (see Table 1).

The overlap-like QMSM Euclidean distances can be used as a descriptor of the dissimilarity between the electron distributions in gas phase and in solution. In this respect, the anions are the species having the largest changes upon solvation, except for the series of H_2O . In the series of NH_3 and H_2S the ordering of solvent-induced perturbation is anion > neutral > cation, while for the series of CH_3NH_2 and CH_3OH it is anion > cation > neutral. The surprising behavior of the H_2O series, where the neutral species is more perturbed than the anion, can be explained as resulting from the bond polarity in the neutral species and the large concentration of charge in the anion.

It should be noted that there is not any inconsistency between the orderings of solvent-induced perturbation determined from the volume and the overlap-like QMSM parameters, since the two measures give different information. Thus, the volume mainly depends on the movement of the outermost electrons, while the regions with the largest electron density (near the nuclei) have the greatest influence in the calculation of the overlap-like QMSM.

The effect of hydration on the Coulombic repulsion interactions follows two different trends, according to the Euclidean distances (Table 2). Thus, the Coulombic repulsion decreases when going from the anion to the cation for the series NH_3 , H_2O , and H_2S , while the cation experiences a slightly larger change than the neutral molecule for the series CH_3NH_2 and CH_3OH . Similar results are obtained from inspection of the MEP. The methyl group generally makes the polarization of ions easier in terms of electrostatic interactions, but for neutral species the behavior of oxygen-based and nitrogen-based species is different.

4. Conclusions

This study illustrates the potential application of the molecular similarity techniques to the study of a wide range of chemical phenomena, like the solvation of molecules, whose complexity requires the use of different computational tools to gain a finer understanding of the chemical process. In this study, the quantum molecular similarity measures have allowed us to perform a quantitative description of the characteristics of the hydration effect on anionic, neutral, and cationic species. The measure of the molecular similarity in terms of the overlap-like or Coulomb-like operators provides information on different aspects of the charge density redistribution induced upon solvation. When this information is taken in conjunction with that provided by other types of calculations such as the molecular volume or the MEP, a detailed picture of the solvent effect on the solute charge redistribution can be achieved.

Present results demonstrate the extreme complexity of the solvent polarization effect on the solute charge distribution. It

is shown that there is not a unique parameter to describe solvent-induced changes, since the solvent might have a differential effect on the electron distribution depending on the specific region of space. As a result, changes in electron distribution can lead to negligible changes in some molecular parameters, while other molecular descriptors can change dramatically. The results reported in this paper reveal that different methods should be used to gain a better understanding of the solvent polarization effect in molecular systems.

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