CSR Chemical Science Reporter
The Orissa Chemical Society e-Magazine

Chemical Science Reporter
An Open-Access e-Magazine of the Orissa Chemical Society

FEBRUARY 28 2020 ISSUE 1

INVITED ARTICLE

Expanding the Frontiers of Non-covalent Interactions

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Dedicated to 80th Birth Anniversary of Prof. Anadi Charan Dash

Abstract: Non-covalent interactions are critical in maintaining the structural integrity of large molecules such as proteins, nucleic acids, and many supramolecular building blocks. One of such interaction is H-bond. Our group is always fascinated to understand the nature and strength of H-bonding interaction that involves sulfur and selenium despite their low electronegativity. The strength of such non-conventional H-bonds is very similar to that of their oxygen analogs. It is found that dispersion and polarizability play a crucial role in explaining such unusual behavior. Also to this, we have shown the existence of hydrogen bond in metal hydrides despite having electropositive metal center as H-bond donor. They also form strong H-bonds with S and Se and are dispersive in nature. Not only H-bond but also we looked at the ubiquitous presence of C-bond in proteins and its importance in myoglobin dissociation. More interestingly, we explored a bi-directional non-covalent interaction in the crystal structure of substituted propellane that arises due to synergistic contributions from C-bond and H-bond, and we named it a *carbo-hydrogen bond*.

Keywords: non-covalent interaction, hydrogen bond, carbon bond, tetrel bond, carbo-hydrogen bond

Introduction

Developing an adequate picture for the understanding of chemical bonds has been a major challenge for the past few centuries. According to IUPAC Gold Book-"*When forces acting between two atoms or groups of atoms lead to the formation of a stable, independent molecular entity, a chemical bond is considered to exist between these atoms or groups. The principal characteristic of a bond in a molecule is the existence of a region between the nuclei of constant potential contours that allows the potential energy to improve substantially by atomic contraction at the expense of only a small increase in kinetic energy*."[1] Interactions between atoms and molecules can result in the formation of either a new molecule (reactive channel) or a molecular cluster (non-reactive channel). The former involves breaking and making bonds called covalent bonds. These bonds involve the sharing of electron pair(s) between two atoms. The latter one is called non-covalent interaction.[2] Non-covalent interaction was first recognized by van der Waals, which later helped him to formulate the famous van der Waals equation for real gases.[3] There is a lot of diversity in the types of non-covalent bonds that attract molecules towards each other. Although some of these interactions, such as hydrogen bonds, are quite familiar in the chemistry lexicon, our understanding of these bonds is still evolving. The idea of H-bonds has been expanded to other atoms too. There is a range of atoms which can replace hydrogen as the bridge. Atoms from Group 15, 16, and 17 can act as a bridge to form non-covalent bonds which are known as pnicogen, chalcogen, and halogen bonds, respectively.[4,5,6] For a complete description of non-covalent interactions both theoretical and experimental approaches are required.[2]

At NISER, most of our work is concentrated at elucidating various types of non-covalent interactions using computational and state-of-art experimental methods.

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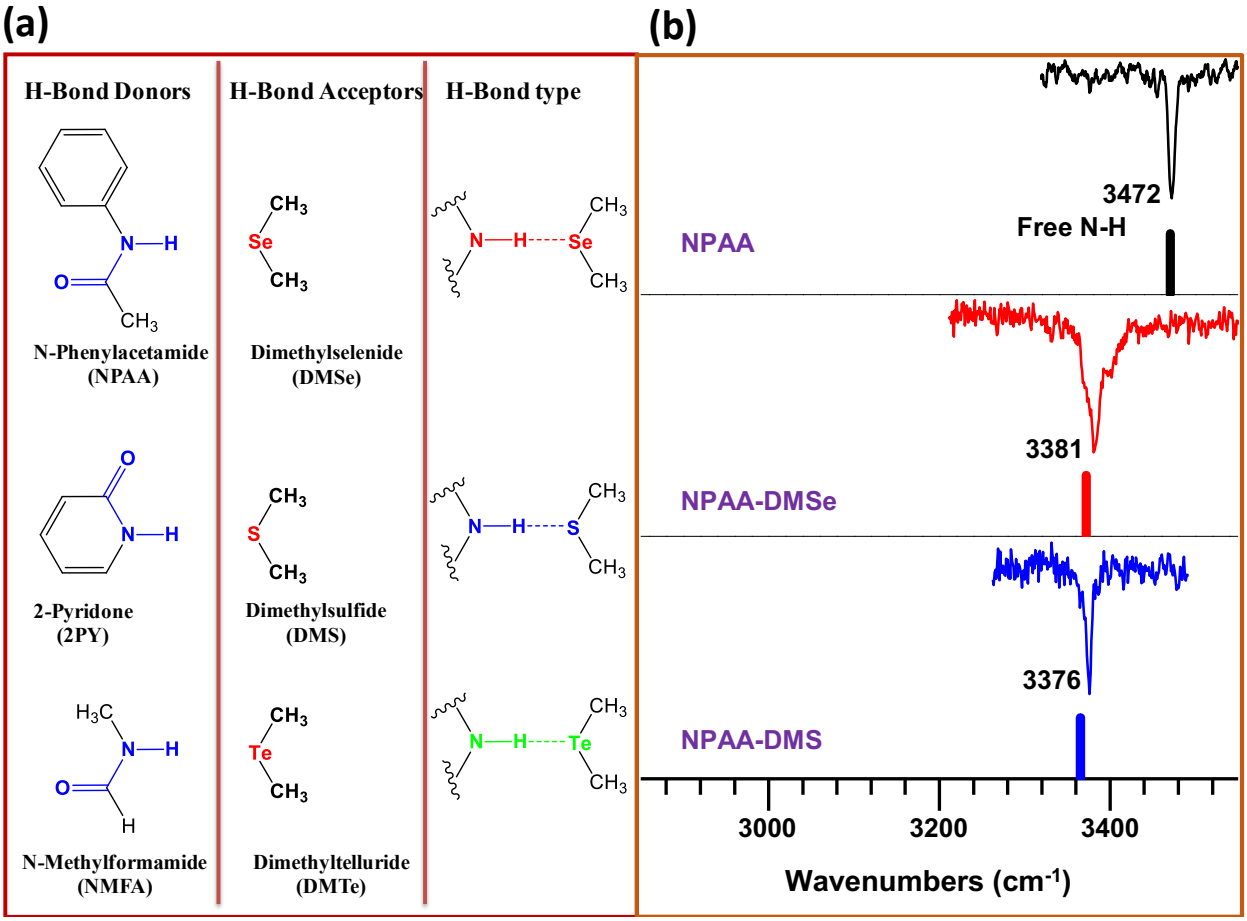

Figure 1 (a) Model compounds of biomolecules, H-bond donors are *N*-phenylacetamide (NPAA), 2-pyridone (2-PY) and N-methylformamide (NMFA), H-bond acceptors are dimethyl selenide (DMSe), dimethyl sulfide (DMS) and dimethyl telluride (DMTe). (b)Gas-phase vibrational spectra of monomer *N*-phenylacetamide (NPAA) and its H-bond complexes with Selenium and Sulfur acceptors in the N-H stretch region, obtained by IR-UV double resonance spectroscopy. Underneath the experimental spectra, DFT-D calculated stick spectra are presented for the sake of comparison and assignment. Reprinted (adapted) with permission from Reference [8], Mundlapati *et al.*, Spectroscopic Evidences for Strong Hydrogen Bonds with Selenomethionine in Proteins, *J. Phys. Chem. Lett.* **2017**, *8*(4), 794-800. Copyright © 2017, American Chemical Society.

DISCUSSION

Establishing the inefficacy of electronegativity in explaining H-bond strength

It was earlier believed that oxygen due to its higher electronegativity can act as a better H-bond acceptor/donor than the lesser electronegative atoms belonging to its group. One of the examples which is most frequently cited to support this fact is that H_2S is a gas whereas H_2O is a liquid at room temperature. However, our experimental and theoretical work on thioamides, methionine and selenomethionine present within biomolecules has proved the erroneous nature of the above conjecture.[7,8] The work was concentrated on H-bonds that were formed between amide N-H as H-bond donor and chalcogen atoms (O, S, Se, Te) as the acceptor (Figure 1a). The computationally found H-bond strengths and experimentally observed shift in N–H stretching frequencies followed the order N–H···S > N–H···Se > N–H···Te > N–H···O (Figure 1b). On the other hand, the electronegativities of O, S, Se and Te follow the order O > S > Se > Te. Hence it is clear that there is no correlation between H-bond strength and electronegativity of the H-bond acceptor atom. Considering the importance of atomic polarizability a parameter was formulated ($\sqrt{|q\sqrt{\alpha}|}$) where q and α are atomic charge and polarisability respectively of the H-bond acceptor atom. This parameter was synchronous with our observations and proved to be a better H-bond descriptor than electronegativity. Our work on thioamides present within proteins and nucleic acids also supported the fact that sulfur has the ability to form stronger H-bonds that oxygen. Both of these works established that electronegativity is not the sole dictator of H-bonds.

H-bonds involving metal hydrides as H-bond donor

Metal hydride carbonyls (such as $Mn(CO)_5H$, $Co(CO)_4H$ and $Fe(CO)_4H_2$, complexes that obey the 18-electron rule) are capable of hydrogen bonds that are comparable to those of the traditional H-bonds.[9] It was shown that interaction between the metal hydride carbonyls forms H-bonds with chalcogen H-bond acceptors like H_2S, H_2Se, H_2O, Me_2S, Me_2Se, and Me_2O. The significance of this work lies in the fact that electronegativities

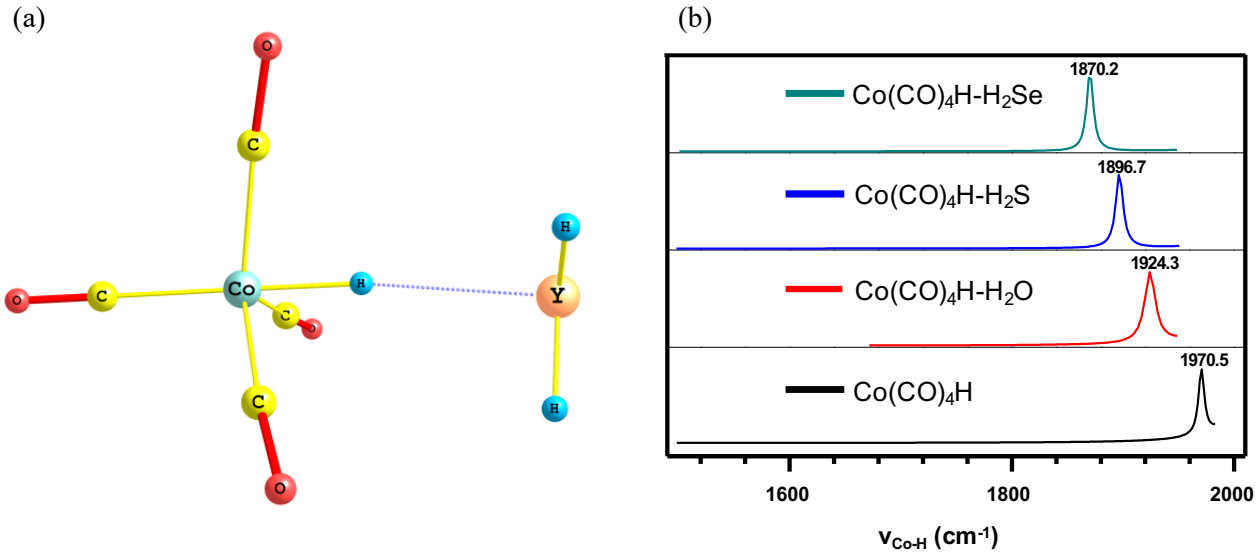

Figure 2 (a) Schematic representation of H-bonding interaction between metal hydride complex and H_2X (where X=O, S, and Se) (b) Simulated vibrational frequencies in free $Co(CO)_4H$ and its complexes $Co(CO)_4H\cdots H_2O$, $Co(CO)_4H\cdots H_2S$, $Co(CO)_4H\cdots H_2Se$.(Reprinted (adapted) with permission from Reference [9], Sahoo *et al.,* Nature and Strength of M–H···S and M–H···Se (M = Mn, Fe, & Co) Hydrogen Bond*, J. Phys. Chem. A.* **2019**, *123*(11), 2227-2236. Copyright © 2019, American Chemical Society.

of Mn, Fe, and Co are less than H atom in M–H bond (H-bond donor), but still, they can form M–H···Y type H-bonds (Figure 2a). It was shown that interaction between the metal hydride carbonyls and electron pair donors is stronger for $(CH_3)_2Se$ than when the donor is $(CH_3)_2O$. The structural, electronic, and energetics of M–H···Y H-bond complexes are very similar to those of conventional O–H···O, N–H···O, and N–H···O=C H-bonds. Figure 2b shows computational M-H stretching frequencies of metal hydride $Co(CO)_4H$ in its free state and its bound state with different H-bond acceptors. The redshift of M-H stretching frequencies for $Co(CO)_4H$-DME, $Co(CO)_4H$-DMS and $Co(CO)_4H$-DMSe complexes are 93, 405, and 408 cm^{-1}, respectively. The stronger the H-bond is, the more likely it is the possibility of an M-H frequency shift (redshift).

In contrast to the conventional H-bonds where electrostatic forces tend to dominate, dispersion forces are the major contributor for these kinds of H-bonds. According to the results, the interaction between the metal hydride carbonyls and electron pair donors is stronger for $(CH_3)_2Se$ than when the donor is $(CH_3)_2O$. This observation is concurrent with our previous work on thioamides, methionine, and selenomethionine where we established that apart from electronegativity, polarizability also plays an important role in determining H-bond strength. This work was recently illustrated in the 3rd edition of the textbook titled '**Inorganic Chemistry**' authored by **Prof. James E. House**.[10]

Carbon Bonding Interactions in Proteins

Carbon bonds are highly directional non-covalent interactions between carbonyl-oxygen acceptors and sp^3-hybridized carbon σ-hole donors through n to σ^* electron delocalization.[11] The objective of the work was to establish the presence of carbon bonds within proteins and estimate their contribution towards structure stabilisation.[12] We have developed in-house python codes to search carbon bonding interactions present within proteins. We searched for carbon bonds of the type Z–$R_3C\cdots O$=C (R=H, C; Z=C, N, O, S) by imposing various geometrical constraints that are adequate for these types of interactions (see Figure 3). Based on $n\rightarrow\sigma^*_{C-Z}$ electron delocalization energy obtained from natural bond orbital analysis (NBO) we proposed an empirical equation which has the ability to predict donor-acceptor interaction (E_{DA}) energy from C···O distance ($d_{C\cdots O}$). In order to evaluate the strength of carbon bonds, we used model molecular systems that mimic C-bonds in proteins. We chose *N,N*-dimethyl acetamide (NNDMA) as the C-bond acceptor mimicking the amide -C=O group in proteins and several C-bond donors bearing different functional groups, such as acetonitrile (ACN), nitromethane (NM), alanine (ALA), acetic acid (AA), acetyl chloride (AcetylCl), and trifluoroacetic acid (TFACE). The C-bond energies (D_0) of the model complexes were calculated by using a very accurate method called CCSD(T) level. From these results, we were able to establish another mathematical relation between D_0 and $d_{C\cdots O}$. This equation can be used to estimate the C-bond energy present within proteins very precisely just by knowing the C···O distances. The range of C-bond energies in proteins are in the range of –2 to –22 $kJmol^{-1}$.

The concept of C-bond can also be used to explain some biophysical phenomena. In a recent report, the ultrafast structural changes in the carbomonoxy myoglobin complex upon photolysis of the Fe–CO bond to the coupling of the ultrafast heme doming mode are attributed to the large-scale modes of the proteins through the low-frequency vibrations.[13] Low-frequency modes of the proteins are generally assigned to the residues which are H-bonded. For example, $Lys^{98}O$-$Lys^{42}N_\xi$ distance shows oscillations with a period of (500±150)fs through an N–H···O=CH-bond. However, these H-bonded resi-

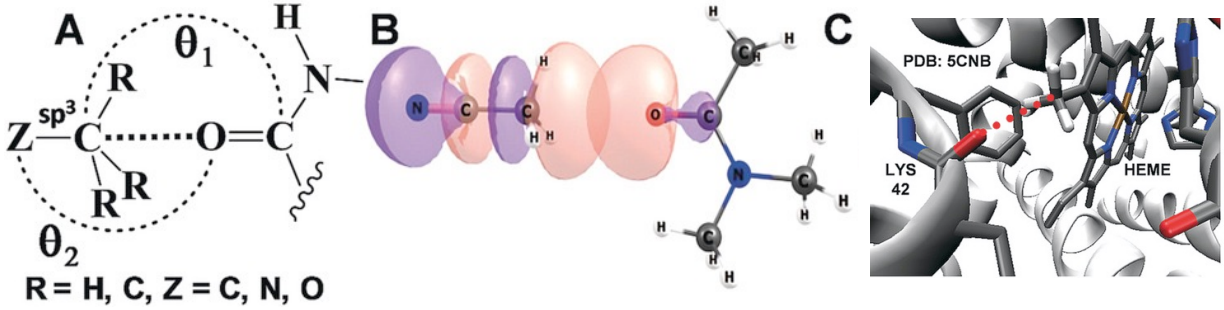

Figure 3 (A) Schematic representation of the carbon bond. **(B)** The C–C···O=C C-bond in NNDMA-ACN characterized by the overlap of p-type carbonyl-oxygen lone pair and C–C σ* orbital, i.e., $n_O \rightarrow \sigma^*_{C-C}$ electron delocalization. **(C)** C–C···O=C C-bond in myoglobin (PDB:5CNB; resolution:1.8Å) formed by Lys^{42}-C=O and heme-CH_3, is responsible for the transmission of the heme doming oscillation directly through Lys42 during CO photolysis in myoglobin to other parts of the protein.

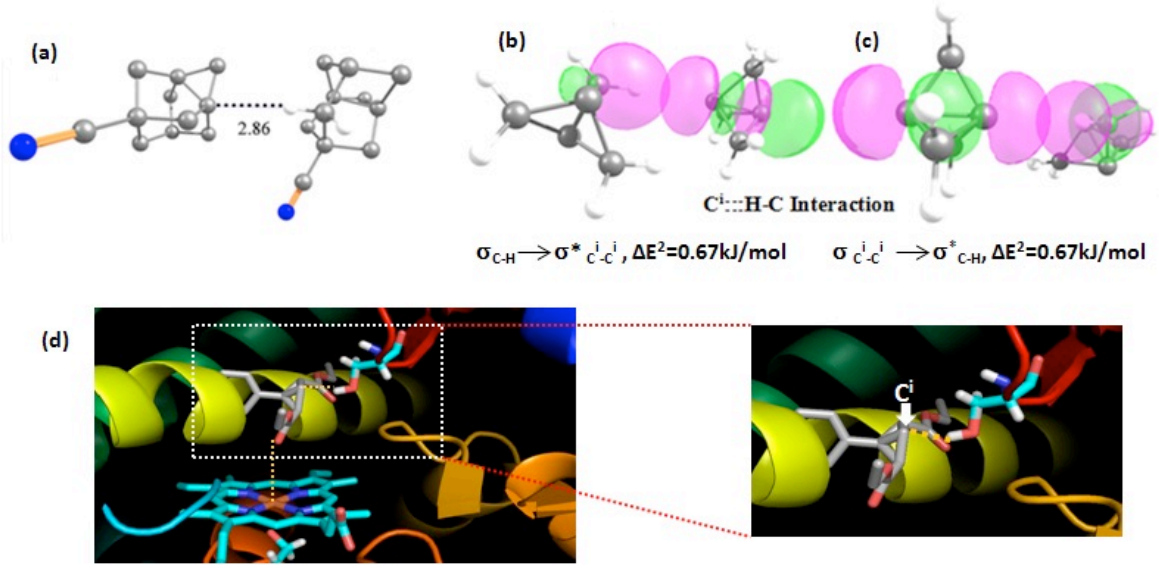

Figure 4 (a) X-ray crystal structure of 5-cyano-1,3-dehydroadamantane (hydrogens are hidden to give a simplified structure). (b) The overlap between σ_{C-H} and $\sigma^*_{C^i-C^i}$ NBOs, and (c) overlap between $\sigma_{C^i-C^i}$ and σ^*_{C-H} NBOs of PPL dimer. (d) The C–C^i:::H–O interaction in cytochrome P411-E10 (PDB ID: 5UCW) formed by the product (bicyclobutane)-C^i–C^i and Ser^{438}–OH, is responsible for the encapsulation of the product in the catalytic center and reduction of product turnover.

dues are located quite far from the heme center and are only connected to the residues near the heme center through multiple H-bonds. Careful observation on the CD corner of the myoglobin reveals the presence of a C···O=C type C-bond which forms a direct connection between Lys^{42} and the heme group. Computational investigation on this C-bond predicted its time period to be 450 fs which is consistent with the ultrafast heme doming mode (417-430fs). Hence the heme doming oscillation can easily be transmitted directly through Lys^{42} to other parts of the protein through a C-bond, which is not discussed in the original report.

A synergy of carbon bond and hydrogen bond: Carbo-Hydrogen bond

Most of the non-covalent interactions discovered to date are unidirectional in nature because they arise due to the interaction of one pair of donor-acceptor electronic orbitals. After a thorough analysis of some crystal structures containing inverted carbon(C^i), we discovered a new type of non-covalent interaction, which is bi-directional in nature. It is the only kind of non-covalent interaction where two pairs of donor-acceptor orbitals are involved. We termed this type of interaction as "Carbo-Hydrogen bond (C_H-bond)" due to the coexistence of both carbon bond and hydrogen bond between two atoms that are not covalently bonded to each other. Initially, we anticipated the existence of this interaction in the crystal structure of 5-cyano-1,3-dehydroadamantane (CCDC 1043567)[14] which contains a C^i–C^i σ-bond in close proximity of a C–H bond of another molecule(Figure 4A). But the quantum chemical calculations of the crystal structure confirmed the presence of a unidirectional C-bond. So in order to investigate the feasibility and existence of C_H-bond in detail, the smallest compound containing inverted carbon:[1.1.1]propellane (PPL) was used as a model compound. NBO calculations of PPL dimer confirmed the presence of C_H-bond which involved two pairs of donor-

acceptor orbitals- (i) bonding σ-orbital of C–H bond and anti-bonding σ*-orbital of C^i–C^i bond (see Figure 4B) and (ii) the bonding σ-orbital of C^i–C^i bond and the anti-bonding σ*-orbital of C–H bond (see Figure 4C). C_H-bond was also found in the complexes of PPL and hydrides of some p-block elements. The non-covalent nature of these interactions was confirmed by various other standard quantum chemical calculations. According to our results, these interactions are stronger than carbon bond but weaker than hydrogen bond (except a few cases). We have also found an instance where C_H-bond aptly explains the abnormal rise in enzymatic activity upon amino acid mutation. In a recent publication entitled "Enzymatic construction of highly strained carbocycles" by Frances H. Arnold and co-workers, have reported the synthesis strained carbocycles with the help of mutated cytochrome P411-E10 that catalyses the formation of chiral bicyclobutane. They observed a higher turnover due to the S438A mutation but provided no reason behind this increased activity. When we looked at the enzyme catalytic site carefully (see Figure 4D), we noticed that there is a possibility of formation of C^i:::H interaction between the side chain of Ser^{438} and inverted carbon (C^i–C^i) of bicyclobutane (product). The C^i:::H bond could be one of the major non-covalent interaction involving Ser^{438} that helps to retain the product in the catalytic site for a longer time and hence reduces the overall turnover number. But when Ser^{438} was replaced by Ala, the C^i:::H bond cannot be possible due to the absence of side chain-OH group and the product can easily be released from the catalytic cycle and thereby yielding more amount of the product.

Conclusion and future perspective

Our initial works have questioned some excessively credulous beliefs in the field of non-covalent bonds. By using an arsenal of spectroscopy and computational methods, we showed that sulfur and selenium in spite of having less electronegativity in comparison to oxygen can form strong H-bonds. Our work on metal hydrides is the first report of its kind where the H-bond donor atom is less electronegative than hydrogen. This work defies the present IUPAC definition which states that H-bond donor atom should be more electronegative than hydrogen. The study on carbon bonds in proteins suggested that they have an important contribution in structure stabilization of proteins and also play a major role in their function. Our most recent work on carbo-hydrogen bond witnessed a rare bi-directional interaction, is an attempt to add a new and unique kind of interaction into the list of non-covalent bonds. We are still thriving to discover and understand various types of non-covalent interactions and their significance in biological and supramolecular chemistry.

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