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Effect of Atomic Charge and Some Physical Properties on pK_a of Substituted Pyridines

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الخلاصة

تضمن البحث تحديد كميات الشحنة على ذرات البريدين لمجموعة من مركبات البريدين أحادية التعويض باستخدام عدد من الطرق المتضمنة على ميكانيك الكم والطرق الحسابية الأساسية وقد أثبتت النتائج التي تم الحصول عليها توافقها مع ما هو معروف بالنسبة لهذا النوع من المركبات من خلال ربطها مع الصفات الكيميائية العملية لهذه المركبات ومن ثم تمت دراسة كمية الشحنة باستخدام ستة نظريات شملت على (MP2,DFT,HF,MNDO,PM3,AM1) ومن ثم ربط هذه القيم مع قيم pK_a لأربعة عشر معوض من معوضات البريدين الأحادية وفي جميع الحالات استخدمت كمية الشحنة على ذرة النتروجين وذرتي الكاربون– الفا كعوامل في عملية التحليل الانحداري وتبين إن أفضل النتائج تم الحصول عليها باستخدام قيم الشحنة لذرة النتروجين المحسوبة بطريقتي AM1, HF مع قيم pK_a كعامل معتمد.

إضافة إلى ذ لك تم استخدام قيم طاقات التكوين لمركبات البريدين أحادية التعويض كعوامل غير معتمدة في عملية التحليل الانحداري مع قيم pK_a.

Abstract

A number of different levels of theoretical calculations have been used for assigning the Mulliken charge to the atoms of mono-substituted pyridines, including both quantum chemical and empirical schemes. A reasonable acceptance for any successful theoretical scheme of calculation is that atomic charges produces should vary in a manner consistent with chemical intuition and more specifically, that these variation should be correlated in a sensible way with experimental observations. The Mulliken charge was calculated using six different theoretical levels (AM1, PM3, MNDO, HF, DFT, MP2). After that the Mulliken charges were tested for their ability to represent variation in the

pK_a values of 14 mono – substituted pyridines. In all cases the Mulliken charge at the nitrogen and the two α – carbon atoms were taken as a representative regression parameters. The Mulliken charge at nitrogen atoms calculated by AM1 and HF levels yielded the most successful correlations with pK_a. Also using other theoretically calculated independent variable such as the heat of formation, leads to improve the correlation with values of pK_a.

Introduction

Although the atomic charge in a molecules is not a proper quantum chemical observed quantity. The idea of assigning charge to atoms has been proven an immensely variable for explanation of a variety of chemical phenomena. On the other hand the atomic charges are important concept in understanding of many type of chemical reactions and they are important parameters in the study of molecular structure properties and activities of reacting molecules. The value of the electron density also it can be used to suggest the most active bonding set in the reacting molecules. According to the above reason different theoretical methods have been proposed for evaluation the electron density (or charges) in the molecules including quantum chemical and empirical methods (1-5).

A reasonable assessment of any calculation scheme can be achieved when the calculated values are very in a manner consistent with the chemical intuition and correlated in a sensible way with experimental observations, such as, Hamitt constant and pK_a's value of the compounds. Many works have been published on the correlation between the value of the pK_a's of some organic molecules, such as anilines (6,7) and benzoic acid (8) and the electron density at the dissociating atoms in the molecules of functional group. On the other hand pyridine is an important molecule provides a good proto-type for assessing substituent effects on the pK_a values of amines. Further more pyridine is relatively small size molecule makes accurate quantum mechanical calculation feasible and allow the discovery of quantum chemical descriptors with accuracy comparable to or better than the empirical Hamett constant. The present work used the most popular theoretical schemes at different levels for the calculation of atomic charge at pyridine atoms together with fourteen substituted pyridine in order to high light the best level can be used for such type of compound. The value of atomic charge and some calculated parameters are then correlated with pK_a's of the compounds.

Methods

To determine the lowest energy conformations for each molecule, geometry optimizations were performed at the AM1 level for several starting geometries in which one or more torsional angles were systematically varied. When multiple low energy geometries were found for compound, HF/(6-31G) single-point energy calculations were performed to determined the most stable conformer. The final geometry optimization for each of the compounds was conducted at the DFT/B3LYP/(6-31G) level. The optimized geometries were used to obtain the Mulliken charge and heat of formation.

On the other hand the pK_a values for all substituted pyridine were taken from literature(9).

Results and Discussions

The Mulliken charge at different atoms of pyridine (Figure I) are calculated using six different levels of theory (AM1, PM3, MNDO, HF, DFT and MP2). These results are tabulated in Table I.

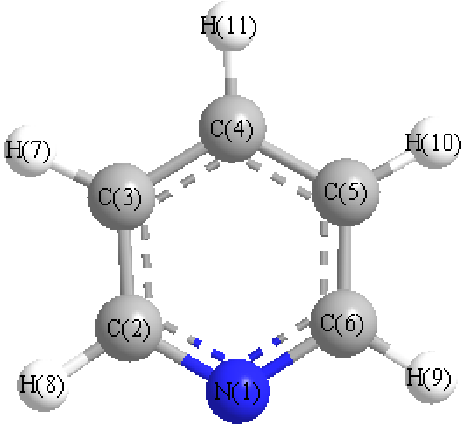

Figure (I): The numbering of pyridine ring atoms

Table I: The Mulliken charges at different pyridine atoms using different theory levels

Methods Atoms	AM1	PM3	MNDO	HF/6-31	DFT/B3 LYP 6-31G	MP2	Max. deferent
N	-0.1381	-0.079	-0.2305	-0.5329	-0.3673	-0.3865	0.5439
C_2 & C_6	-0.072	-0.062	0.0541	-0.0542	-0.0013	-0.007	0.0650
C_3 & C_5	-0.1815	-0.1513	-0.1239	-0.2380	-0.1098	-0.1399	0.1282
C_4	-0.0931	-0.0645	-0.0080	-0.1588	-0.1169	-0.1494	0.1508

These results showed that the charge is highly concentrated at the nitrogen atom which is the most electronegative atom in the pyridine. Further more the charge are suddenly decreased at the two α- carbon atoms to the nitrogen (C_2 & C_6) followed by small increase in the charge as the carbon atom becomes far away from the nitrogen. This result is consistent with fact that the electronegative atom acts as an electron-withdrawing group.(EW. G) (10) which attracted the electron from atoms near to it and this effect decreases as the distance between the atoms increases. Also there is no possibility for conjugation between the lone – pair electrons and π – electron of the aromatic ring(11).

A plot (Figure II) of the charges against the different theoretical levels of calculation show that variations in the charge of carbon atoms are very small compare to the variations in nitrogen charge. On the other hand it is well known that there is a large difference between the electronegativity of the nitrogen and carbon atoms in pyridine. So that we thought that the theoretical methods gave a large differences in charge between α- carbon and the nitrogen could be consider as a best level of calculations. Figure II shows that maximum deference is shown by HF level of calculation while AM1 & PM3 shows the minimum difference. This results is in accordance with our expectation.

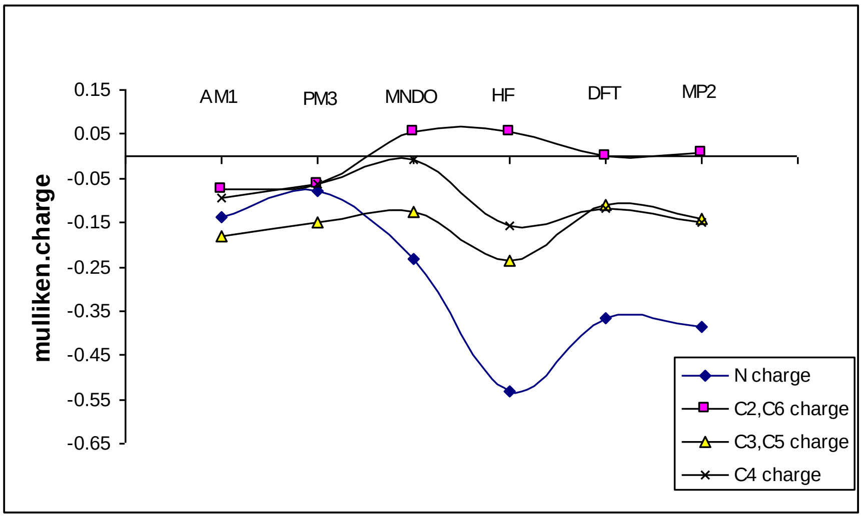

Figure II: The Mulliken charge for pyridine atoms at different theoretical levels

The Mulliken charge at nitrogen and two α- carbon atom are theoretically calculated for fourteen mono substituted pyridines in order to assess the effects of substituent on the charge of these atoms. These results were tabulated in Table II, III and IV.

Table II: represent the Mulliken charge at nitrogen atom for substituted pyridines using different theoretical levels.

Comp. no	Levels Compounds	AM1	PM3	MNDO	HF/ 6-31G	DFT/B3LYP 6-31G	MP2	pKa
1	py	-0.1381	-0.0789	-0.2305	-0.53299	-0.367371	-0.38653	5.31
2	3-Ac	-0.1478	-0.0905	-0.2434	-0.54542	-0.367993	-0.37958	3.26
3	3-Cl	-0.1279	-0.0648	-0.2246	-0.52688	-0.360395	-0.37514	2.83
4	3-CN	-0.1369	-0.0742	-0.2341	-0.53328	-0.36151	-0.37406	1.59
5	3-CO2H	-0.1392	-0.076	-0.236	-0.5392	-0.368659	-0.37491	3.93
6	4-Ac	-0.1189	-0.0562	-0.2055	-0.5123	-0.3807	-0.35368	3.62
7	4-Cl	-0.1355	-0.0799	-0.2229	-0.52466	-0.359403	-0.11499	4.11
8	4-CN	-0.12	-0.2097	-0.2097	-0.51108	-0.344465	0.377984	2.26
9	4-CO2H	-0.1128	-0.0495	-0.2011	-0.50698	-0.383534	-0.35135	4.61
10	4-CHO	-0.1426	-0.0858	-0.225	-0.5391	-0.369295	-0.38606	4.86
11	4-NH2	-0.1824	-0.1392	-0.2717	-0.56408	-0.382159	-0.39508	9.68
12	2-Me	-0.1435	-0.078	-0.2269	-0.56876	-0.403992	-0.41145	5.91
13	3-Me	-0.1354	-0.0744	-0.2332	-0.52958	-0.366188	-0.38766	5.68
14	4-Me	-0.1426	-0.0866	-0.225	-0.53907	-0.369291	-0.38605	6.04
15	4-CH2NH2	-0.1382	-0.0796	-0.223	-0.53632	-0.366951	-0.38516	4.41

Table III: represent the Mulliken charge at C_2 atom for substituted pyridines using different theoretical levels.

Comp. no.	Levels Compounds	AM1	PM3	MNDO	HF/ 6-31G	DFT/B3LYP 6-31G	MP2
1	py	-0.0727	-0.0620	0.0541	0.0542	-0.0013	0.0078
2	3-Ac	-0.0456	-0.0344	0.0853	0.0066	0.0124	-0.0029
3	3-Cl	-0.0719	-0.0636	-0.0633	0.0608	0.0046	-0.0067
4	3-CN	-0.0494	-0.0411	0.0829	0.0808	0.0207	0.0046
5	3-CO2H	-0.0399	-0.0303	0.0910	0.0800	-0.0001	0.0157
6	4-Ac	-0.0818	-0.0745	0.0379	0.0376	-0.0045	-0.0093
7	4-Cl	-0.0629	-0.0475	0.0599	0.0612	0.0046	0.0003
8	4-CN	-0.0727	0.0500	0.0500	0.0512	-0.0012	-0.0019
9	4-CO2H	-0.0841	-0.0769	0.0344	-0.0376	-0.0093	-0.0045
10	4-CHO	-0.0696	-0.0573	0.0496	-0.0609	-0.0014	-0.0102
11	4-NH2	-0.031	-0.0108	0.0933	0.0695	-0.0126	-0.0211
12	2-Me	-0.0652	-0.0561	0.0559	-0.0630	0.0022	0.0067
13	3-Me	-0.0787	-0.0702	0.0583	0.0478	-0.0028	-0.0073
14	4-Me	-0.0697	-0.0570	0.0496	-0.0608	-0.0013	-0.0102
15	4-CH2NH2	-0.0709	-0.0592	0.0473	0.0589	-0.0046	-0.0479

Table IV: Represent the Mulliken charge at C_6 atom for substituted pyridines using different theoretical levels

Comp. no	Levels Compounds	AM1	PM3	MNDO	HF/ 6-31G	DFT/B3LYP 6-31G	MP2
1	py	-0.0727	-0.062	0.0541	0.054228	-0.00137	0.007861
2	3-Ac	-0.0323	-0.024	0.0998	0.08745	-0.022212	-0.02155
3	3-Cl	-0.0617	-0.061	0.0781	0.109765	0.035574	0.022562
4	3-CN	-0.0296	-0.0285	0.101	0.121469	0.037074	0.030355
5	3-CO2H	-0.0379	-0.0328	0.0931	0.085661	0.00667	-0.02748
6	4-Ac	-0.0826	-0.0748	0.0388	0.044567	-0.007268	-0.00618
7	4-Cl	-0.063	-0.0475	0.0599	0.06133	0.00469	0.000304
8	4-CN	-0.0727	0.05	0.05	0.051218	-0.001362	-0.03461
9	4-CO2H	-0.0826	-0.0748	0.0388	0.040092	-0.00814	-0.00314
10	4-CHO	-0.0697	-0.0571	-0.0493	0.058925	-0.003798	-0.01176
11	4-NH2	-0.031	-0.0108	0.0933	0.069567	-0.012527	-0.02117
12	2-Me	-0.011	-0.0342	0.0191	0.229619	0.189561	0.165231
13	3-Me	-0.074	-0.0651	0.0705	0.045595	-0.031622	-0.02236
14	4-Me	-0.0697	-0.0571	0.0493	0.058873	-0.003778	-0.01177
15	4-CH2NH2	-0.0709	-0.0605	0.0473	0.055792	-0.004616	-0.0121

These results mainly show that there is an electron condensation at the nitrogen atom of the ring which is the most electronegative atom in the molecule. On the other hand substituent effects can be divide in to two category. The electron withdrawing group decreases the electron density at the pyridine ring as the case of compounds (no.7,8) and via versa for the electron donating group as in case of compound (no.11, 14). This result is consistent with the well known chemical facts(10). Although the electron density on the pyridine nitrogen is very low and it is insensitive(Figure III) it can be used in correlation with pK_a of the compounds in order to assist the effect of substituent (11).

Table (III & IV) show the electron density at C_2 & C_6 of pyridine molecule and is substituted compounds.

These result showed a different in the value between C_2 & C_6 in case of substituted pyridine due to the an symmetry of the molecule while the pyridine substituted in position 4 the two values of C_2 & C_6 almost the same with small difference on using AM1, MP3 and MNDO levels. While we found a large deferences in case of HF, DFT and MP2 this may be due to the sensitivity on these levels.

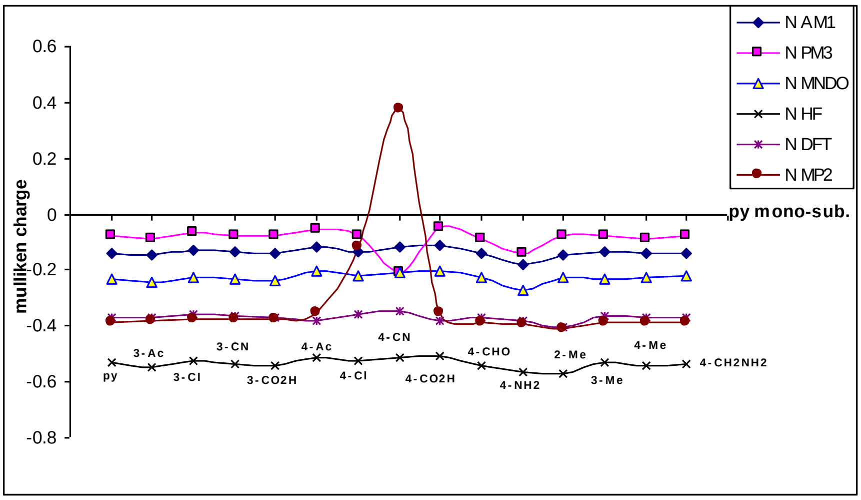

Figure (III): The variation of Mulliken charge of nitrogen atom for mono-substituted pyridine using different theoretical levels

The variation in the electron density of the two α- carbon atoms are also insensitive to the substiteunt charge as shown in the Figures (IV,V).

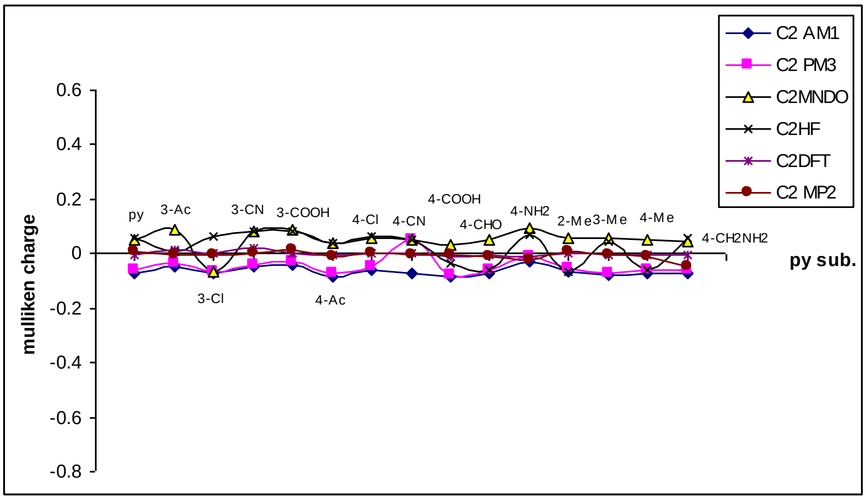

Figure (IV): The variation of Mulliken charge of C_2 carbon atom for mono-substituted pyridine using different theoretical levels

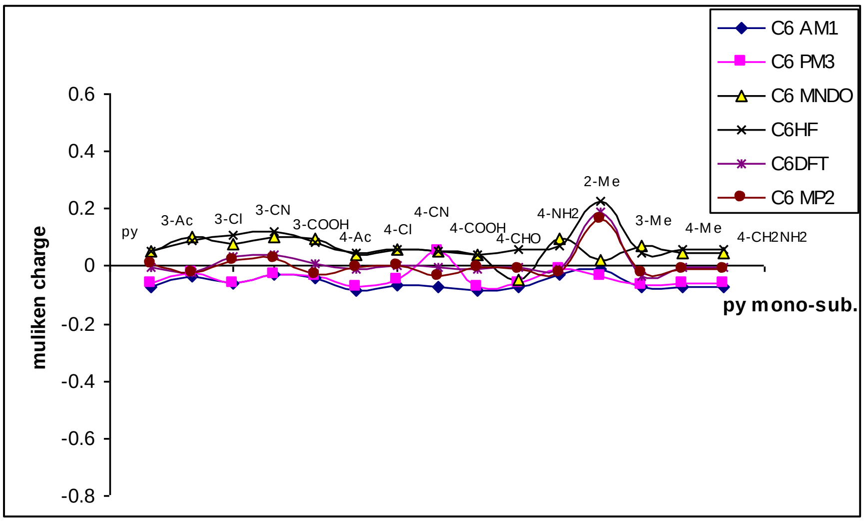

Figure (V): The variation of Mulliken charge of C_6 carbon atom for mono-substituted pyridine using different theoretical levels

On the other hand the heat of formation was calculated using DFT/ B3PYL/6-31G and HF/6-31G for 14- mono-substituted pyridine and gathered at Table (V).

Table (V): Represent heat of formation for substituted pyridines using DFT and HF levels

Comp. no	Levels Compounds	DFT B3PYL / 6-31G	HF / 6-31 G
		H_f(kcal/mol)	H_f(kcal/mol)
1	py	-248.060	-246.594
2	3-Ac	-400.576	-398.293
3	3-Cl	-707.5725	-705.799
4	3-CN	-340.224	-338.279
5	3-CO2H	436.482	-434.104
6	4-Ac	-400.576	-398.293
7	4-Cl	-705.469	-707.573
8	4-CN	-340..223	-338.277
9	4-CO2H	-436.481	-434.118
10	4-CHO	287.341	-285.617
11	4-NH2	-301.608	-303.375
12	2-Me	-287.343	-285.619
13	3-Me	-287.34	-285.615
14	4-Me	287.341	-285.616
15	4-CH2NH2	-342.628	-340.608

H_f = heat of formation,

Correlations

The six different theoretical values of Mulliken charges were examined for their ability to correlate with the experimental pK_a values for a series of 14 mono-substituted pyridines. The charge investigated are those belong to the nitrogen and two α-carbon atoms in the pyridine ring. These results of regression analysis were shown in Table VI, VII and VIII.

Table VI: Regression statistics for pK_a as dependent variable versus the nitrogen Mulliken charge as independent variable using six different theoretical levels

no	Constants Levels	a	b	R
1	AM1	-7.233	85.649	0.707
2	PM3	4.282	-2.924	0.059
3	MNDO	-10.076	-64.246	0.556
4	HF	-30.473	-65.569	0.588
5	DFT	-24.376	-78.124	0.547
6	MP2	3.440	-3.521	0.370

Table VII: Regression statistics for pK_a as dependent variable versus the C_2 Mulliken charge as independent variable using six different theoretical levels

no	Constants Levels	a	b	R
1	AM1	6.418	29.161	0.238
2	PM3	4.237	-6.583	0.109
3	MNDO	3.791	14.294	0.274
4	HF	4.749	-8.102	0.226
5	DFT	4.594	-159.211	0.671
6	MP2	4.330	-36.116	0.275

Table VIII: Regression statistics for pK_a as dependent variable versus the C_6 Mulliken charge as independent variable using six different theoretical levels

no	Constants Levels	a	b	R
1	AM1	2.381E-2	-2.918	0.190
2	PM3	0.248	1.437	0.133
3	MNDO	0.186	5.199E-2	0.006
4	HF	0.206	-0.219	0.031
5	DFT	0.190	-0.139	0.021
6	MP2	0.191	-0.597	0.084

In general these results show that the nitrogen charge gives better correlations with the pK_a than the charge of the two α-carbon atoms, which reveals a considerable agreement with the fact that protonation reaction are occurred at the nitrogen atom of the pyridine ring making the most effective factor is the charge of nitrogen atom (5).

However the nitrogen charge varied with pK_a intuitively i.e the pk_a increased as the nitrogen charge become more negative suggesting that a nitrogen associated with more electron density more readily accepts a proton. Compared to the nitrogen in pyridine Mulliken charge (-0.53299, pK_a = 5.31) while nitrogen in 2-methyl pyridine Mulliken charge (-0.56876, pK_a= 5.91) at HF level.

On the other hand the value of regression coefficient (R) for nitrogen charge vs the pK_a' s ranging between 0.7 for AM1 level and 0.05 for MP2 while the value of R for the α-carbon atoms ranging between (0.1-0.09) again suggesting that the most effective factor for determination the value of pK_a is the charge on the nitrogen atoms. The correlation between pK_a' s as dependent variable versus the nitrogen atom charges and heat of formation for the compounds under investigation leads to an improvement the values of the regression factor (R) as show in Table(IX).

Table (IX): Regression statistics for pK_a as dependent variable versus the H_f, and nitrogen atom charges as independent variable using DFT and HF levels

Methods / Parameters	HF/6-31G			DFT/B3PYL/6-31G		
	a	b	R	a	b	R
$N_{\text{Mull. Charge}}$	-30.473	-65.569	0.588	-24.376	-78.124	0.547
H_f	5.681	3.28E-3	0.380	6.556	5.20E-3	0.382
$N_{\text{Mull. Charge}}$ H_f	-25.913	-58.369 2.056E-3	0.631	-19.386	-68.181 3.38E-3	0.596

Conclusion

A variety of methods exit for calculating partial atomic charges in the molecules. To gauge their usefulness one should be demonstrate that this parameter can be used to account for substituent effects in addition to their ability to quantitively relate the electronic properties of substituent to their physiochemical effects. The variation of calculated atomic charge appeared to be intuitive in the sense that they suggested that an increase in the pyridine pK_a was accompanied by an increase in the negative charge on the nitrogen atom. And from the correlation of some parameters derived from quantum chemical calculations we conclude that these parameters have reached a stage at which they can make useful contributions to the analysis of pK_a of the pyridines. On the other hand using different theoretical levels of calculation showed no clear evidence about the most applicable level since all levels showed the same trend of variation with more sensitivity in case HF and DFT levels.

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