Kinetic Studies on the Structure-Reactivity of Aryl Dithiomethylacetates

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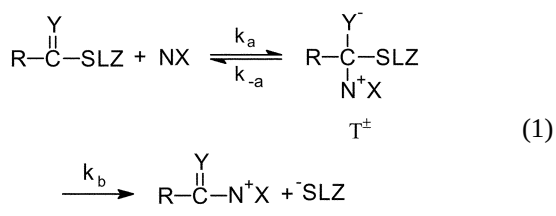
Kinetic studies of the pyridinolysis (XC_5H_4N) of aryl dithiomethylacetates ($CH_3CH_2C(=S)SC_6H_4Z$, **1**) are carried out in acetonitrile at 60.0 °C. A biphasic Brönsted plot is obtained with a change in slope from a large ($\beta_X \cong 0.8$) to a small ($\beta_X \cong 0.2$) value at $pK_a^o = 5.2$, which is attributed to a change in the rate limiting step from breakdown to formation of a zwitterionic tetrahedral intermediate, $T^{\pm}$, in reaction path as the basicity of the pyridine nucleophile increases. This mechanism is supported by the change of the cross-interaction constant ρ_{XZ} from a large positive ($\rho_{XZ} = +1.36$) for the weakly basic pyridines to a small negative ($\rho_{XZ} = -0.22$) value for the strongly basic pyridines. The magnitudes of ρ_Z and activation parameters are also consistent with the proposed mechanism.

Key Words : Nucleophilic substitution reaction, Pyridinolysis, Cross-interaction constant, Zwitterionic tetrahedral intermediate, Stepwise mechanism

Introduction

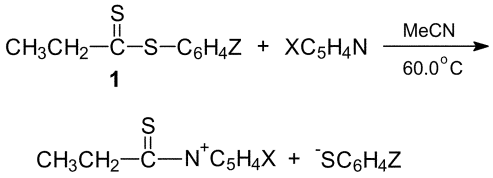
The mechanisms of the aminolysis of aryl esters and carbonates have been well established.[1] These reactions are known to proceed stepwise through a zwitterionic tetrahedral intermediate, $T^{\pm}$. The existence of the intermediate has been deduced from curved Brönsted-type plots. A biphasic dependence of the rate on the amine basicity showing a change of slope from a large ($\beta_{nuc} \geq 0.8$) to a small ($\beta_{nuc} \approx 0.1$-0.3) value at pK_a^o, where the amine and leaving group have the same expulsion rates from $T^{\pm}$, has been attributed to a change in the rate-limiting step from breakdown to formation of a tetrahedral intermediate as the basicity of the amine increases.[2-5]

The aminolysis of dithio esters and carbonates has been studied in aqueous and acetonitrile solutions.[6] An important advantage of using an acetonitrile medium is that there are no complications arising from a kinetically important proton transfer from $T^{\pm}$ to the amine.[7] In water, the rate of proton transfer, k_H, may be faster than that of expulsion of arenethiolate from $T^{\pm}$ so that the rate law becomes complex.[7] This kinetic complexity encountered in the aminolysis of dithiocarboxylates (and also thiono) compounds in water is known to originate from the weak π bond energy of CS (compared to CO) which causes the difficulty in reforming the CS double bond when $T^{\pm}$ break down expelling either the amine or ArS^-.[7]



(1)

The breakpoint, pK_a^o, has been shown to depend on various factors which influence the relative rates of expulsion of the nucleophile, amine, (k_{-a}) and leaving group (k_b) from a tetrahedral intermediate,[8,9] k_{-a}/k_b in eq. (1). Keeping other conditions constants the breakpoint, pK_a^o, occurs at a lower pK_a value due to a decrease in k_{-a}/k_b: (i) as the leaving ability of ^-SLZ increases,[10] (ii) as the nonleaving R becomes stronger electron donating group,[11] (large k_b), (iii) as the amine nature changes successively from a primary (*e.g.* benzylamine) → secondary (alicyclic) → aniline → pyridine[12] (successive decreases in k_{-a}/k_b), (iv) by substituents of S^- for O^- in $T^{\pm}$, *i.e.*, for thiono than carbonyl esters,[13] (decrease in k_{-a} more than k_b), (v) in aqueous than aprotic solvent[14] (decrease in k_{-a}).



(2)

X = 4-CH_3O, 4-CH_3, 3-CH_3, 4-$C_6H_5CH_2$, H, 3-C_6H_5, 3-CH_3CO, 3-Cl, 4-CH_3CO, 4-CN, and 3-CN
Z = 4-CH_3, H, 4-Cl, and 4-Br

In this work, we report the result of kinetic studies on the pyridinolysis of aryl dithiomethylacetates in acetonitrile at 60.0 °C, eq. (2). The aim is to complete the previous studies[15] on the aminolysis mechanism of aryl dithiomethylacetates and to further clarify the influence of the amine nature on the pK_a^o value. As an additional criterion for the elucidation of the mechanism, we determined the cross-interaction constant,[16] ρ_{XZ}, in eqs. (3a) and (3b), where X and Z represent substituents in the nucleophile and leaving group, respectively.

$$\log(k_{XZ}/k_{HH}) = \rho_X\sigma_X + \rho_Z\sigma_Z + \rho_{XZ}\sigma_X\sigma_Z \quad (3a)$$

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Table 1. The Second Order Rate Constants, k_N ($\times 10^3$ M^{-1} s^{-1}), and Selectivity Parameters,[a] ρ_X, ρ_Z, ρ_{XZ}, β_X, for the Reaction of Z-Phenyl Dithiomethylacetates with X-Pyridines in Acetonitrile at 60.0 °C

X	pK_a	Z				ρ_Z[h]
		4-CH_3	H	4-Cl	4-Br	
4-CH_3O	6.47	5.57	7.89	11.3	14.1	0.89 ± 0.14
4-CH_3	6.00	4.27	6.05	8.43	10.5	0.85 ± 0.13
3-CH_3	5.68	3.41	4.75	6.79	8.29	0.86 ± 0.12
4-$C_6H_5CH_2$	5.59	3.29	4.58	6.42	7.92	0.85 ± 0.12
H	5.17	2.74	3.79	5.19	6.44	0.82 ± 0.13
3-C_6H_5	4.87	1.33	2.25	3.42	4.51	1.16 ± 0.17
3-CH_3CO	3.26	0.0571	0.119	0.207	0.335	1.64 ± 0.30
3-Cl	2.84	0.0427	0.0855	0.154	0.250	1.65 ± 0.30
4-CH_3CO	2.38	0.0142	0.0267	0.0523	0.0830	1.67 ± 0.28
4-CN	1.90	0.00427	0.00785	0.0159	0.0281	1.76 ± 0.35
3-CN	1.45	0.00208	0.00468	0.00909	0.0139	1.81 ± 0.26
ρ_X[b,c]		-1.12 ± 0.04	-1.17 ± 0.04	-1.21 ± 0.08	-1.23 ± 0.06	ρ_{XZ}[b,i] = -0.22
β_X[b,d]		0.24 ± 0.14	0.25 ± 0.01	0.26 ± 0.01	0.27 ± 0.01	
ρ_X[e,f]		-4.30 ± 0.18	-4.13 ± 0.11	-3.89 ± 0.09	-3.67 ± 0.09	ρ_{XZ}[e,j] = +1.36
β_X[e,g]		0.82 ± 0.02	0.78 ± 0.02	0.74 ± 0.02	0.71 ± 0.03	

[a]The *s* values were taken from C. Hansch, A. Leo, and R. W. Taft, *Chem. Rev.* **1991**, *91*, 165. The pK_a values of pyridine in water at 25 °C were taken from: (a) Albert, A.; Serjeant, E. P. *The determination of Ionization Constants;* 3rd ed.; Chapman and Hall: New York, 1984; pp 154-155. (b) Dean, J. A. *Handbook of Organic Chemistry*; McGraw-Hill: New York, 1987; Chapter 8. (c) Fischer, A.; Galloway, J. A.; Vaughan, J. *J. Chem. Soc.* **1964**, 3591. (d) The pK_a values of X=3-C_6H_5 and X=4-CH_3CO were taken from ref 25. [b]For X=4-CH_3O, 4-CH_3, 3-CH_3, 4-$C_6H_5CH_2$, and H [c]Correlation coefficients are better than 0.996 in all cases. [d]Correlation coefficients are better than 0.995 in all cases. [e]For X=H, 3-C_6H_5, 3-CH_3CO, 3-Cl, 4-CH_3CO, 4-CN, 3-CN. [f]Correlation coefficients are better than 0.998 in all cases. [g]Correlation coefficients are better than 0.996 in all cases. [h]Correlation coefficients are better than 0.973 in all cases. [i]Correlation coefficient is 0.975. [j]Corelation coefficient is 0.995.

$$\rho_{XZ} = \partial\rho_X/\partial\sigma_Z = \partial\rho_Z/\partial\sigma_X \quad (3b)$$

Results and Discussion

The rate law obtained in the present reactions is given by eqs. (4) and (5), where ArS^- is the leaving group, k_{obs} is the pseudo-first-order rate constant, k_0 and k_N are the rate constants for solvolysis and pyridinolysis of the substrate, respectively, and [Py] and [S] represent the pyridine and substrate concenturations, respectively. The value of k_0 was negligible in acetonitrile, $k_0 \cong 0$.

$$d[ArS^-]/dt = k_{obs}[S] \quad (4)$$

$$k_{obs} = k_0 + k_N[Py] \quad (5)$$

The second-order rate constants for pyridinolysis (k_N) were obtained as the slopes of plots of eq. (5). These values, together with those of the pK_a of the conjugate acids of the pyridines, are summarized in the Table 1. The rate of aryl dithiomethylacetate with pyridine nucleophiles (*e.g.* k_N = 3.79×10^{-3} $M^{-1}s^{-1}$ at 60.0 °C with Z = H) are slower than aryl dithioacetate with pyridine (k_N = 5.08×10^{-3} $M^{-1}s^{-1}$ at 60.0 °C with Z = H).[15] The higher rates observed with CH_3 than C_2H_5 can be explained by the steric effect of the ethyl group. The Brönsted plots using the k_N and pK_a values in Table 1 were obtained as presented in Figure 1. The slopes are collected in Table 1, where the Hammett coefficients, $\rho_X(=\rho_{nuc})$ and $\rho_Z(=\rho_{lg})$, and the cross-interaction constant, ρ_{XZ}, are also presented. Close examination of ρ and β values, shows that the magnitude of ρ_X and β_X are somewhat larger

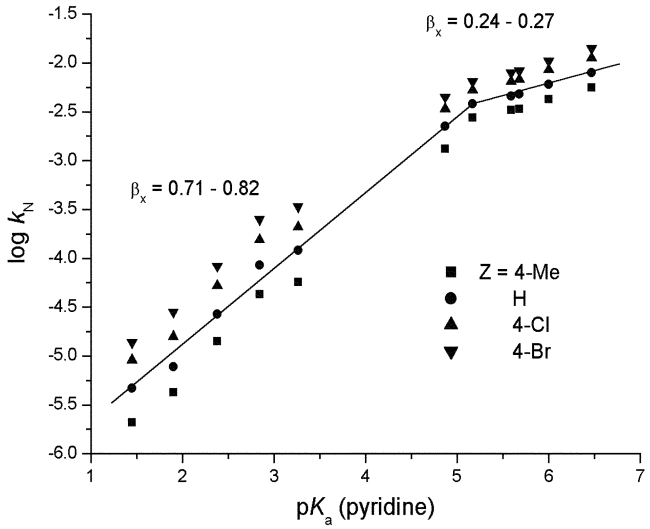

Figure 1. Brönsted plots for the reactions of Z-aryl dithiomethylacetates with X-Pyridines in acetonitrile at 60.0 °C.

with CH_3 than that with C_2H_5. These differences reflect that the TS with CH_3 is somewhat tighter than that with C_2H_5. Although the β_X values are based on the plots of log k_N(MeCN) vs pK_a(H_2O), they can provide reasonable guides since a near constant ΔpK_a (= pK_a(MeCN) – pK_a(H_2O) ≅ 7.5) was experimentally[17] as well as theoretically[18] found and the slopes will remain practically the same irrespective of whether pK_a(H_2O) or pK_a(MeCN) is used in the Brönsted correlation. We note that the Brönsted plots in Figure 1 are biphasic with a change in the slope. For Z = H the slope

changes from $\beta_X = 0.78$ to 0.25 at the breakpoints $pK_a^o = 5.2$ as the basicity of pyridine increases. The magnitude of β_X is somewhat smaller than those ($\beta_X \geq 0.8$)[19] normally obtained but is well within the range ($\beta_X \geq 0.7$-0.8 in water[20] and 0.6-0.7 in acetonitrile[21]) of the corresponding values for the stepwise reactions with rate-limiting expulsion of leaving group. For example, in the aminolysis of ethyl S-aryl thiolcarbonates with secondary alicyclic amines in water the slopes were $\beta x = 0.7$-0.8,[20] and in the pyridinolysis of S-phenyl 4-nitrobenzoates in acetonitrile the slopes were $\beta x = 0.6$-0.7,[21] both which were consistent with a stepwise mechanism where the breakdown of a zwitterionic tetrahedral intermediate, $T^{\pm}$, is rate-determining. The $\beta x = 0.25$ obtained for more basic pyridines in Table 1 is also consistent with a stepwise mechanism in which the formation of $T^{\pm}$ is rate-limiting.[19a] In the pyridinolysis of aryl dithioacetates, $CH_3C(=S)SC_6H_4Z$, a biphasic plot with a change of slope from $\beta x \cong 0.9$ to a small value of $\beta x \cong 0.4$ was observed with a breakpoint at $pK_a^o = 5.2$.[22]

On the other hand, in the reactions of **1** the βx values were 1.5-2.8 and 0.9-1.2 with benzylamines (at -35.0 °C) and anilines (at 45.0 °C), respectively[15] and no breakpoints were observed. This means that the breakpoints are at $pK_a^o \geq 9.7$ (the highest pK_a used; 4-methoxybenzylamine) and $pK_a^o \geq 5.4$ (the highest pK_a used; 4-methoxyaniline) for the reactions with benzylamines and anilines, respectively. The decreasing pK_a^o value which is related to the decrease in the k_{-a}/k_b ratio in the order benzylamine (≥ 9.7) > aniline (≥ 5.4) > pyridine (=5.2) is consistent with the general sequence of the rate of amine expulsion (k_{-a}) from the tetrahedral intermediate, primary amines > secondary alicyclic amines > anilines > pyridines.[23] For the aminolysis of **1** the breakpoint, pK_a^o(=5.2), can be experimentally observed only in the reactions with pyridines since the pK_a^o value is higher than the basicities of amines used in the reactions with benzylamines and anilines. This is why a biphasic plots with a clear-cut breakpoint, pK_a^o, is often observed in the aminolysis with pyridine nucleophiles, as in the pyridinolysis of aryl dithioacetates[21] and aryl dithiomethylacetates in this work, both at $pK_a^o = 5.2$. There are other reasons of the relatively low pK_a^o value (=5.2) for the two pyridinolysis of the dithio series: (i) Thiono (S^-) rather than carbonyl (O^-) series leads to a lower pK_a^o due to a decrease in the k_{-a}/k_b ratio, since the lower proclivity of S^- than O^- in $T^{\pm}$ to form a double bond and expel a leaving group leads to a slower amine expulsion from $T^{\pm}$ (smaller k_{-a}) relative to ArS^- leaving (k_b).[1] For example, the reactions of benzylamines with S-phenyl acetates,[24] $CH_3C(=O)SC_6H_4Z$, in acetonitrile proceed by a stepwise mechanism with rate-limiting expulsion of $ZC_6H_4S^-$ leaving group ($pK_a^o \geq 9.7$) from $T^{\pm}$ but those with aryl dithioacetates, $CH_3C(=S)SC_6H_4Z$ (2), proceed by rate-limiting formation of $T^{\pm}$ [25] ($pK_a^o \leq 9.14$; the lowest pK_a used; 4-chlorobenzylamine) (ii) Thiophenoxide leaving groups ($ZC_6H_4S^-$) used have lower basicities than phenoxide leaving groups ($ZC_6H_4O^-$) for the same Z, and hence k_b should be greater (decrease in k_{-a}/k_b) leading to a lower pK_a^o than the corresponding esters with a phenoxide leaving group.[26]

In contrast there are also other factors in favor of a higher pK_a^o for the present reaction series: (i) Aprotic solvent, MeCN, favors amine expulsion (larger k_{-a}) to form ester compared to aqueous solution by stabilizing the TS for the breakdown of $T^{\pm}$ to form uncharged products relative to that for the formation of anionic leaving group and cationic amide.[14] This will raise the k_{-a}/k_b ratio and hence leads to a higher pK_a^o value, (ii) An electron donating acyl group, R, results in a rate increase[27] in the stepwise reactions where leaving group expulsion is rate-determining, but favors the expulsion of amine relative to thiophenoxide anion, *i.e.*, k_{-a}/k_b increase.[11] In the reactions of aryl dithio series, $RC(=S)SC_6H_4Z$, with anilines, R = C_2H_5 renders a greater rate, $k_N = 3.19 \times 10^{-3}\ M^{-1}s^{-1}$ (Z = H), at 45.0 °C relative to R = CH_3 ($k_N = 9.46 \times 10^{-4}\ M^{-1}s^{-1}$ at 50.0 °C, Z = H) and R = C_6H_5 ($k_N = 2.85 \times 10^{-3}\ M^{-1}s^{-1}$ at 55.0 °C, Z = H).[15] This means that the ethyl group is a stronger electron acceptor than either R = CH_3 or C_6H_5 group and hence the k_{-a}/k_b ratio should be greater with a higher pK_a^o value than that for the aryl dithio series with R = CH_3 and C_6H_5. This is indeed evidenced by the mechanistic change over from rate-limiting breakdown of $T^{\pm}$ with anilines to a stepwise mechanism with rate-limiting formation of $T^{\pm}$ (*i.e.*, pK_a^o is at lower values) in the aminolysis of the two dithio compounds (R = CH_3[25] and C_6H_5[6]) with benzylamines in contrast to no mechanistic change, *i.e.*, the stepwise with rate-limiting breakdown of $T^{\pm}$, for the aminolysis of ethyl[15] series, with anilines and benzylamines. The pK_a^o observed (=5.2) is then the consequence of balance between these two opposing effects on the k_{-a}/k_b ratio.

The size of ρ_Z in Table 1 also reflects the mechanistic change. The magnitudes of ρ_Z change from larger values, $\rho_Z = 1.2$-1.8, for less basic pyridines to smaller values, $\rho_Z \cong 0.8$ for more basic pyridines, which is in agreement with the decrease in bond cleavage a the rate-determining step switches from breakdown to formation of the intermediate. Such decrease in the magnitude of the ρ_Z values from large ($\rho_Z = 2.4$-3.2) to small values ($\rho_Z = 2.3$) with the mechanistic change is also reported in the pyridinolysis of aryl dithioacetates.[22] Rough estimate of the $\beta_Z(=\beta_{lg})$ values shows a decrease from $\beta_Z \cong -0.5$ to 0.3 at the breakpoint in agreement with the change in the rate-determining step.

Another important results that support mechanistic change at $pK_a^o = 5.2$ from breakdown to formation of $T^{\pm}$ as the basicity of pyridine is increased is a clear-cut change in the cross-interaction constant from a relatively large positive, $\rho_{XZ} = +1.36$, to a small negative value, $\rho_{XZ} = -0.22$, at the breakpoint. Similar changes of the ρ_{XZ} values have been reported for the pyridinolysis of S-phenyl 4-nitrobenzoates,[21] $4\text{-}NO_2C_6H_4C(=O)SC_6H_4Z$, and aryl dithioacetates,[24] $CH_3C(=S)SC_6H_4Z$. In the former the ρ_{XZ} value change from +1.41 to 0.32 at $pK_a^o \cong 4.2$ and in the latter from +1.34 to -0.15 at $pK_a^o = 5.2$ as the basicity of pyridine is increased. These are of course interpreted to indicate mechanistic changes from breakdown to formation of $T^{\pm}$. These changes in the ρ_{XZ} values with changes in the mechanism of reaction

Table 2. Activation Parameters[a] for the Reactions of Z-Phenyl Dithiomethylacetates with X-Pyridines in Acetonitrile

X	Z	t (°C)	k_N ($\times 10^3$ M^{-1} s^{-1})	$\Delta H^{\neq}$ (kcal mol^{-1})	$-\Delta S^{\neq}$ (cal mol^{-1} K^{-1})
4-CH_3O	4-CH_3	60.0	5.57	5.6	52
		50.0	4.09		
		40.0	3.04		
4-CH_3O	4-Br	60.0	14.1	5.3	51
		50.0	10.5		
		40.0	7.93		
3-Cl	4-CH_3	60.0	0.0427	5.7	62
		50.0	0.0312		
		40.0	0.0228		
3-Cl	4-Br	60.0	0.250	5.8	58
		50.0	0.185		
		40.0	0.135		

[a]Calculated by the Eyring equation. The maximum errors calculated (by the method of K. B. Wiberg, Physical Organic Chemistry, Wiley, New York, 1964, p 378.) are ± 0.6 kcal mol^{-1} and ± 2 e.u. for $\Delta H^{\neq}$ and $\Delta S^{\neq}$, respectively.

provide further credence to the cross-interaction constant as a useful mechanistic criterion.

The activation parameters determined with the rate constants at three temperatures are shown in Table 2. The activation enthalpies are low ($\Delta H^{\neq} \cong 6$ kcal/mol), and activation entropies have large negative values ($\Delta S^{\neq}$ = -51 to -62 cal mol^{-1} K^{-1}). The large negative $\Delta S^{\neq}$ values (from -58 to -62 cal mol^{-1} K^{-1}) for the weakly basic pyridine (X = 3-Cl) are in accord with the rate-limiting expulsion of the leaving group since the soft ArS^- groups formed in the TS are solvated by the soft aprotic solvent (MeCN) molecules.

We have confirmed that the aminolysis of aryl dithiomethylacetates in acetonitrile proceeds by a stepwise mechanism through a zwitterionic tetrahedral intermediate, $T^{\pm}$, with rate-limiting expulsion of the thiophenoxide (ArS^-) group by observing the breakpoint at pK_a^o = 5.2 due to change in the rate-limiting step associated with the intermediate, $T^{\pm}$. The relatively low pK_a^o value is ascribed to the stability of the tetrahedral intermediate where the decrease in k_{-a} is greater than that in k_b with Y = S relative to that with Y = O. The mechanistic change from rate-limiting expulsion of the leaving group from $T^{\pm}$ to formation of the intermediate is well defined by a change in the cross-interaction constants ρ_{XZ} from a large positive value (+1.36) to a small negative value (-0.22).

Experimental Section

Materials. Merk GR acetonitrile was used after three distillations. The pyridine nucleophiles, Aldrich GR, were used without further purification.

Substrates. Preparations and analytical data are reported elsewhere.[15]

Kinetic measurement. Rates were measured conductometrically in acetonitrile. The conductivity bridge used in this work was a homemade computer-automatic A/D converter conductivity bridge. Pseudo-first-order rate constants, k_{obs}, were determined by the Guggenheim method with large excess of pyridine (Py). Second order rate constants, k_2, were obtained from the slope of a plot of k_{obs} *vs* [Py] with more than five concentrations of pyridine. The k_2 values in Table 1 are the averages of more than three runs and were reproducible to within ± 3%.

Product analysis. Substrate, p-bromophenyl dithiomethylacetate (0.05 mole) was reacted with excess 4-picoline (0.5 mole) with stirring for more than 15 half-lives at 60.0 °C in acetonitrile. The salt was filtered and solvent was removed from the precipitate. Analysis of the product gave the following results.

$CH_3CH_2C(=S)N^+C_5H_4$-*p*-$CH_3^-SC_6H_4$-4-Br: m.p. 58-61 °C, ^{1}H NMR (400 MHz, $CDCl_3$), 2.35 (3H, s, CH_3), 2.91 (1H, q, CH_2), 7.31-7.34 (4H, m, phenyl), 8.45-8.85 (4H, m, pyridine); ^{13}C NMR (100.4 MHz, $CDCl_3$), 227.1 (C=S), 135.7, 135.1, 132.4, 132.1, 131.5, 129.4, 123.5, 122.9, 121.5, 26.1 (CH_3); ν_{max} (KBr), 1567, 1455 (C=C, phenyl), 1229 (C=S), 855 (C-H, pyridine), 801 (C-H, phenyl); mass, m/z 402 (M^+). Anal. Calcd for $C_{19}H_{16}BrNS_2$; C, 56.7; H, 4.01. Found; C, 56.5; H. 4.03.

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