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Variations of Tautomeric Preferences in Histamine Monocation – Ab initio Studies for "Essential" and "Scorpio" Conformations from the Gas Phase to Aqueous Solution

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The polarizable continuum model (PCM) for geometries optimized at the RHF/6-31G* was applied to study the variations of the tautomeric preferences in the histamine monocation from the gas phase to aqueous solution. Seven solvents of different polarities (from cyclohexane to water) were chosen and calculations performed. A change of the tautomeric preference takes place already in apolar solvents containing heteroatoms. The ring N-aza protonated form (ImH^+) is only favoured in the gas phase and cyclohexane,ś benzene, CCl_4. The chain N-amino protonated form (AmH^+-T_1) predominates in other solvents: $CHCl_3$, THF, acetone, water.

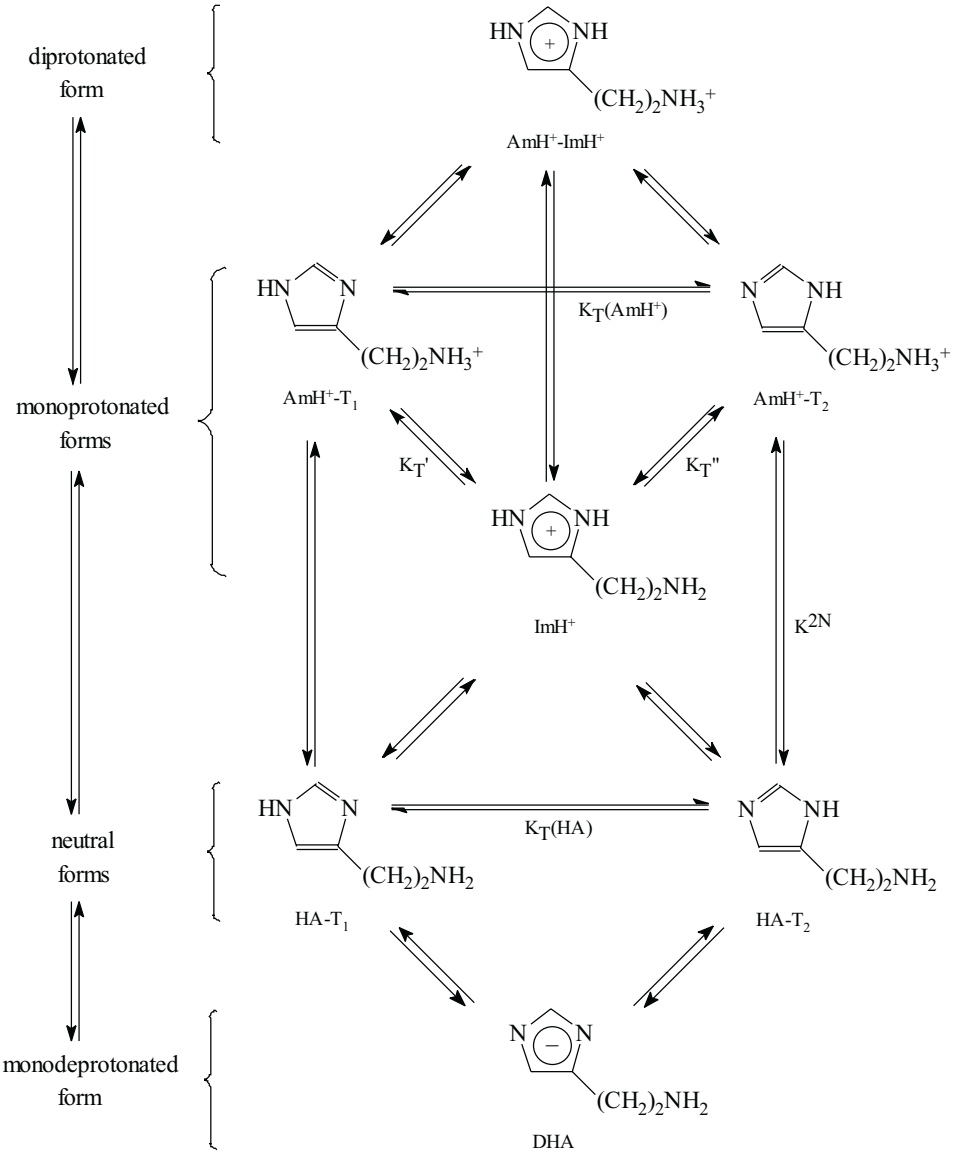
Key words: histamine monocation, relative energies, solvation effect, *ab initio* calculations

Histamine – a biogenic amine – displays a complicated system of different protonated, tautomeric and conformational states (Scheme 1), which play an important role in interactions of histamine with specific receptors [1–4]. Various experimental and computational techniques were applied to resolve the problem of histamine structure, but there are no common conclusions. This is the reason for which the relations between the structure of histamine and its biological activity are not yet well established.

In the previous paper, it has been shown [5] that rotational isomerism and intramolecular interactions possible in the neutral forms of histamine (HA-T_1 and HA-T_2) strongly influence the prototropic tautomerism and basicity. The proton-transfer reactions depend also on environment. The tautomeric preference in the monoprotonated forms in the gas phase is not the same as in aqueous solution [6]. Contrary to the gas phase that favours the ImH^+ form in the monocationic mixture [7,8], the AmH^+-T_1 tautomer predominates in aqueous solution [9]. This situation encouraged us to undertake investigations on the proton-transfer reactions for the histamine monocation in different solvents to find the conditions (properties of solvent) in which the variation takes place.

For our studies, the same two stable conformations (*trans* called 'essential' – favoured in aqueous solution [9], and *gauche* called 'scorpio' – proposed in the gas phase [7,10]) were selected as in the previous paper [6]. *Ab initio* calculations were performed using the RHF/6-31G* method [11]. This level of theory has been found to be sufficient for investigations of the proton-transfer reactions in histamine [6].

It predicts the same tautomeric preferences for isolated molecules as high level MP and QCID methods. To study the solvation effect on the prototropic tautomerism in the histamine monocation, seven solvents of different polarities (from cyclohexane to water) and the polarizable continuum model (PCM) [12–14] were chosen. In the PCM, the geometries optimized at the RHF/6-31G* were used. This model gives reasonable results for polyfunctional nitrogen bases [6,15]. Relative energies were estimated for isolated as well as for solvated molecules. Variations of the tautomeric preferences when proceeding from the gas phase to aqueous solution were discussed.



Scheme 1. Proton-transfer reactions in histamine.

METHODS

Ab initio calculations for two selected conformations: 'essential' and 'scorpio' (*trans* and *gauche* given in Fig. 1) of the monoprotonated histamine were realized at the RHF/6-31G* level [11] using the Gamess program [16]. The geometries of all species were fully optimized without symmetry constraint and the stationary point on the potential energy surface found. All geometrical parameters were the same as previously described [6].

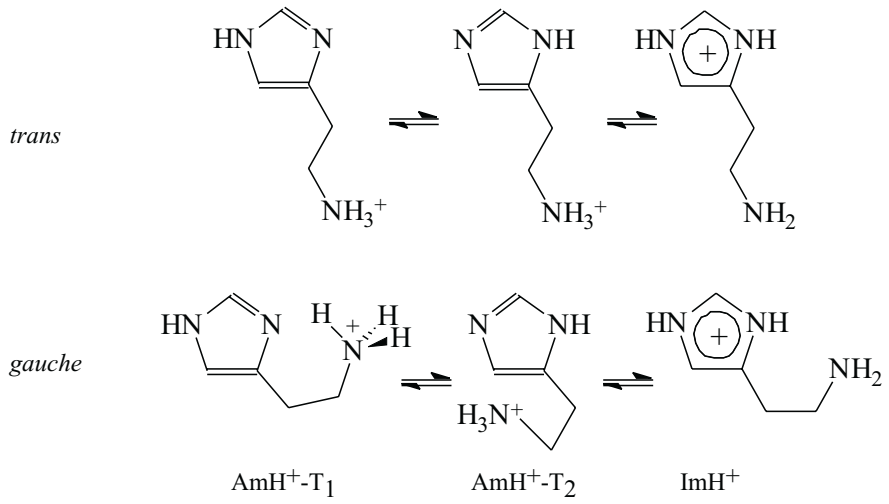


Figure 1. The *trans* and *gauche* conformations for the histamine monocation.

Thermal corrections to the enthalpy and entropy were calculated and included to the Gibbs free energies. In these calculations, the ideal gas equation-of-state, temperature of 298.15 K, and pressure of 1 atm were assumed. The total energies of individual tautomers are given in Table 1. The relative thermodynamic parameters for tautomerization process (ΔQ in kcal mol^{-1}, 1 cal = 4.184 J) calculated according to (1): ΔE – relative total energies, $\Delta H°$ – relative enthalpies, $\Delta G°$ – relative free energies, and pK_T derived from the $\Delta G°$ according to (2) and (3) are listed in Table 2. The factor of 2.303RT is equal to 1.3643 for standard conditions (T = 298.15 K).

$$\Delta Q = Q(T_i) - Q(T_j) \quad (1)$$

$$pK_T(AmH^+) = [\Delta G°(AmH^+\text{-}T_1) - \Delta G°(AmH^+\text{-}T_2)]/2.303RT \quad (2)$$

$$pK'_T = [\Delta G°(AmH^+\text{-}T_1) - \Delta G°(ImH^+)]/2.303RT \quad (3)$$

Effects of solute solvent interactions on the tautomeric preferences for two selected stable conformations (*trans* and *gauche*) of the histamine monocation were studied using the PCM method (which partially includes specific solvation) [12–14] and the geometries optimized at the RHF/6-31G* level. The total and relative energies calculated in 7 solvents are listed in Table 1 and 3, respectively. Variations of the dipole moments in all ionic forms of histamine when proceeding from the gas phase to aqueous solution are given in Table 4.

Table 1. Total energies (a.u.) calculated for the histamine monocationic tautomers in the gas phase and solution using the PCM model and geometries optymized at the RHF/6-31G* level.

Phase	*trans*			*gauche*		
	AmH^+-T_1	AmH^+-T_2	ImH^+	AmH^+-T_1	AmH^+-T_2	ImH^+
gas [a]	–358.290079	–358.271790	–358.295815	–358.309991	–358.278656	–358.315077
cyclohexane	–358.339711	–358.327929	–358.341762	–358.353537	–358.331446	–358.355669
benzene	–358.344844	–358.333877	–358.346448	–358.357929	–358.336954	–358.359691
CCl_4	–358.344442	–358.333408	–358.346084	–358.357586	–358.336522	–358.359381
$CHCl_3$	–358.370844	–358.364291	–358.370090	–358.379874	–358.365170	–358.379603
THF	–358.379013	–358.373750	–358.377458	–358.386597	–358.374072	–358.385661
acetone	–358.388850	–358.386219	–358.386241	–358.394669	–358.384948	–358.392772
H_2O	–358.393473	–358.391424	–358.390211	–358.398312	–358.390103	–358.395847

[a] RHF/6-31G*.

RESULTS AND DISCUSSION

Extended *ab initio* calculations were realized at the RHF/6-31G*//6-31G* level for the same two conformations (*trans* and *gauche*) of the histamine monocation as previously described [6]. Calculations indicate that the thermal corrections are almost the same for individual tautomers. The differences in their values are not larger than 1 kcal mol^{-1}. This means that (i) the relative enthalpies (ΔH°) and the relative free energies (ΔG°) corresponding to 298.15 K are not very different from the relative total energies (ΔE°) corresponding to 0 K (Table 2), (ii) the tautomerization processes in the histamine monocation, where the proton is transferred between atoms of the same element from the amino to the imino nitrogen atom, seems to be slightly dependent on temperature.

Table 2. Thermodynamic parameters (ΔE, ΔH°, ΔG° and pK_T) for tautomerization process in the *trans* and *gauche* conformations of the histamine monocation calculated at the RHF/6-31G*//6-31G* level.

Property	*trans*	
	(1-2) [a]	(1-3) [b]
ΔE (in kcal mol^{-1})	–11.5	3.6
ΔH° (in kcal mol^{-1})	–11.4	4.7
ΔG° (in kcal mol^{-1})	–10.9	4.5
pK_T	–8.0	3.3
	gauche	
ΔE (in kcal mol^{-1})	–19.7	3.2
ΔH° (in kcal mol^{-1})	–19.7	3.9
ΔG° (in kcal mol^{-1})	–19.0	3.8
pK_T	–13.9	2.8

[a] Relative parameter between the AmH^+-T_1 and AmH^+-T_2 tautomers. [b] Relative parameter between the AmH^+-T_1 and ImH^+ tautomers.

The ImH^+ tautomer predominates in the monocationic mixture for both, the *trans* and *gauche* conformations in the gas phase. The AmH^+-T_1 tautomer (very important in aqueous solution [9]) has larger Gibbs free energy than the ImH^+ by *ca.* 4 kcal mol^{-1}. This difference in energies depends slightly on conformation, but it is sufficiently high that the contribution of the AmH^+-T_1 in the gas phase is very low (<0.5 %). The AmH^+-T_2 tautomer has exceptionally high Gibbs free energy (larger than the T_1 by more than 10 kcal mol^{-1}), and thus its contribution in monocationic mixture in the gas phase ($<10^{-6}$ %) can be neglected.

Among two stable conformations considered for the ImH^+, the 'scorpio' (*gauche*) conformation has lower Gibbs free energy in the gas phase than the 'essential' one (*trans*) by 10.4 kcal mol^{-1}. Similar difference in Gibbs free energies (11.1 kcal mol^{-1}) is found between the 'scorpio' and 'essential' conformations of the less favourable AmH^+-T_1. This means that the intramolecular hydrogen bonding between the protonated and free nitrogen basic functions called 'internal' solvation [10,17] is very important in the gas phase and influences the basicity of bidentate nitrogen ligands. Comparison of the experimental gas-phase basicities (GB) of 4(5)-methylimidazole and histamine indicates that this interaction increases the GB value of histamine by 11.3 kcal mol^{-1} [10,18]. Such type of enhancement of the gas-phase basicity has been observed for other bidentate nitrogen ligands (*e.g.* diamines, amidinamines, guanidinamines) [17–19].

Interactions with solvent molecules may change or even eliminate the internal effects and change basic properties of individual tautomers. These effects influence the tautomeric equilibria and the contribution of each tautomer in the tautomeric mixture. To study the variations of tautomeric preferences in the histamine monocation when proceeding from the gas phase to aqueous solution and to estimate the external effects of the solute-solvent interactions, the PCM method was applied to geometries optimized at the RHF/6-31G* level. For calculations, seven solvents of different polarities: cyclohexane ($\varepsilon = 2.023$), benzene ($\varepsilon = 2.247$), CCl_4 ($\varepsilon = 2.228$), $CHCl_3$ ($\varepsilon = 4.900$), THF ($\varepsilon = 7.580$), acetone ($\varepsilon = 20.700$), and water ($\varepsilon = 78.390$) were chosen. The relative energies calculated between the ionic forms in seven solvents are listed in Table 3.

Table 3. Relative total energies (kcal mol^{-1}) between monoprotonated histamine tautomers in the gas phase and solution calculated using the PCM model and geometries optymized at the RHF/6-31G* level.

Phase	$(\varepsilon-1)/(2\varepsilon+1)$ [c]	ΔE(1-2) [a]		ΔE(1-3) [b]	
		trans	*gauche*	*trans*	*gauche*
gas [d,e]	0	–11.5	–19.7	3.6	3.2
cyclohexane	0.20	–7.4	–13.9	1.3	1.3
benzene	0.23	–6.9	–13.2	1.0	1.1
CCl_4	0.23	–6.9	–13.2	1.0	1.1
$CHCl_3$	0.36	–4.1	–9.2	–0.5	–0.2
THF	0.41	–3.3	–7.9	–1.0	–0.6
acetone	0.46	–1.7	–6.1	–1.6	–1.2
H_2O [e]	0.49	–1.3	–5.2	–2.0	–1.6

[a] $\Delta E(1\text{-}2) = E(AmH^+\text{-}T_1) - E(AmH^+\text{-}T_2)$. [b] $\Delta E(1\text{-}3) = E(AmH^+\text{-}T_1) - E(ImH^+)$. [c] Kirkwood and Onsager macroscopic dielectric function [12,13]. [d] RHF/6-31G*//6-31G*. [e] As in [6].

Perusal of the relative energy values (ΔE) indicates that the variations of the tautomeric preferences in the histamine monocation are very large. The ΔE(1-2) values calculated between the AmH^+-T_1 and AmH^+-T_2 tautomers vary by more than 10 kcal mol^{-1}, when going from the gas phase to aqueous solution, *i.e.* from –11.5 kcal mol^{-1} to –1.3 kcal mol^{-1} for the *trans* conformation, and from –19.7 kcal mol^{-1} to –5.2 kcal mol^{-1} for the *gauche* conformation. So high variation may result from the presence of the positive charge on the chain N-amino in the AmH^+-T_1 and AmH^+-T_2 tautomers. This charge influences the electron-withdrawing effect of the ethylamino group. Partial neutralization of this charge by solvent dipoles reduces the electron-withdrawing effect of the side chain, and in consequence, decreases the difference between basicities of the T_1 and T_2 tautomers. Smaller difference between basicities of individual tautomers induces lower ΔE values. The external interactions of both tautomers of the AmH^+ do not change the sign of the ΔE(1-2), and thus do not change the site of the mono- (the chain N-amino) and diprotonation (the ring N-imino). When proceeding from the gas phase to aqueous solution, the basicity of the N-imino in the AmH^+-T_1 seems to be always lower than that in the AmH^+-T_2 {negative ΔE(1-2)}, and thus the AmH^+-T_1 is more favoured than the AmH^+-T_2.

Quite a different situation is for the relative energies calculated between the AmH^+-T_1 and ImH^+ tautomers: (i) the E(1-3) changes the sign for both conformations (*trans* and *gauche*) in solvents containing heteroatoms and possessing hydrogen bonding donor or acceptor properties, (ii) variations of the ΔE(1-3) are considerably smaller than those of the ΔE(1-2) for the AmH^+ tautomers.

The change of the sign in the ΔE(1-3) when going from the gas phase (positive) to aqueous solution (negative) indicates that the site of protonation is not the same. The ring N-imino is only favoured in the gas phase and apolar solvents (cyclohexane, benzene and CCl_4). The chain N-amino predominates in other solvents containing heteroatoms ($CHCl_3$, THF, acetone, water). Such kind of solvents reduce the polarizability of the imidazole ring, decrease the basicity of the N-imino, and in consequence, change the favoured site of protonation. This behaviour is common for both conformations (*trans* and *gauche*).

Variations of the ΔE(1-3) are twice smaller than those between the AmH^+-T_1 and AmH^+-T_2 tautomers. The ΔE(1-3) values vary by *ca.* 5–6 kcal mol^{-1} when proceeding from the gas phase to aqueous solution, *i.e.* from 3.6 kcal mol^{-1} to –2.0 kcal mol^{-1} for the *trans* conformation, and from 3.2 kcal mol^{-1} to –1.6 kcal mol^{-1} for the *gauche* conformation. These variations indicate that the difference between the basicities of the ring N-imino and the chain N-amino is not very large. In aqueous solution, the pK_a value corresponding to the protonation of the chain N-amino (10.1) in the T_1 tautomer of the neutral histamine is larger than that for the ring N-imino protonation (7.5) by 2.6 pK_a units (3.5 kcal mol^{-1} at 298.15 K) [1]. This fact is in good agreement with the PCM results. According to recent FT-IR and Raman experiments [9], the AmH^+-T_1 tautomer has been detected in water solution, for which the *trans* conformation has been proposed. However, both conformations (*trans* and *gauche*) have been identified in NMR spectra [20]. The PCM method indicates a lower energy for the *gauche* than *trans* conformation of the AmH^+-T_1 tautomer by *ca.* 3 kcal mol^{-1}.

The ΔE(1-2) and ΔE(1-3) in various phases correspond to the differences between basicities of the protonation sites or between acidities of the deprotonation site in individual tautomers (Scheme 1). Strength of the basic or acidic site depends on the localization of the partial charges in the molecule. Some kind of information on a localization (or separation) of the charge gives the dipole moment (μ). Comparison of the μ values calculated for all monocationic histamine species using the PCM model and geometries optymized at the RHF/6-31G* level (Table 4) indicates that the higher variations of the μ are for both conformation of the AmH^+-T_2 tautomer. This tautomer is the most polar one, and its polarity strongly varies with the polarity of the solvent. Therefore, in each phase the difference between the μ values of the AmH^+-T_1 and AmH^+-T_2 {Δμ(1-2)} is higher than that between the AmH^+-T_1 and ImH^+ {Δμ(1-3)} independently on the conformation of the alkyl chain (Table 5). When proceeding from the gas phase to aqueous solution, variations of the Δμ(1-2) are higher than those of the Δμ(1-3). This may explain smaller variations of the ΔE(1-3) than ΔE(1-2).

Table 4. Dipole moments (Debyes) calculated for the histamine monocationic tautomers in the gas phase and solution using the PCM model and geometries optymized at the RHF/6-31G* level.

Phase	*trans*			*gauche*		
	AmH^+-T_1	AmH^+-T_2	ImH^+	AmH^+-T_1	AmH^+-T_2	ImH^+
gas [a,b]	9.79	15.62	7.16	4.70	10.70	3.20
cycklohexane	10.36	16.75	7.70	5.03	11.51	3.49
benzene	10.43	16.89	7.76	5.07	11.61	3.52
CCl_4	10.42	16.88	7.76	5.07	11.60	3.52
$CHCl_3$	10.78	17.64	8.09	5.28	12.16	3.71
THF	10.89	17.89	8.21	5.34	12.35	3.78
acetone	11.03	18.26	8.34	5.44	12.60	3.86
H_2O [a]	11.11	18.40	8.39	5.48	12.72	3.89

[a] As in 6. [b] RHF/6-31G*//6-31G*.

Table 5. Relative dipole moments (Debyes) between monoprotonated histamine tautomers in the gas phase and solution calculated using the PCM model and geometries optymized at the RHF/6-31G* level.

Phase	Δμ(1–2) [a]		Δμ(1–3) [b]	
	trans	*gauche*	*trans*	*gauche*
gas [c,d]	–5.8	–6.0	2.6	1.5
cyclohexane	–6.4	–6.5	2.7	1.5
benzene	–6.5	–6.5	2.7	1.6
CCl_4	–6.5	–6.5	2.7	1.6
$CHCl_3$	–6.9	–6.9	2.7	1.6
THF	–7.0	–7.0	2.7	1.6
acetone	–7.2	–7.1	2.7	1.6
H_2O [d]	–7.3	–7.2	2.7	1.6

[a] $\Delta\mu(1\text{-}2) = \mu(AmH^+\text{-}T_1) - \mu(AmH^+\text{-}T_2)$. [b] $\Delta\mu(1\text{-}3) = \mu(AmH^+\text{-}T_1) - \mu(ImH^+)$.
[c] RHF/6-31G*//6-31G*. [d] As in 6.

Since the PCM method is based on the Kirkwood and Onsager model for the solute-solvent interactions [12–14], the relative energies (Table 3) vary linearly with the macroscopic dielectric function of Kirkwood and Onsager, KO = (ε – 1)/(2ε + 1). It is not surprizing that variations of the ΔE are relatively large in solvents of low polarity (ε<15), and they become less important in more polar solvents [21–23]. Therefore, the ΔE values strongly vary when going from the gas phase (ε = 1) to THF (ε = 7.580), but in water (ε = 78.390) they are not very different from those in acetone (ε = 20.700). Parameters calculated for the linear regression between the ΔE and KO function are given in Table 6. Slope of the regression line is a kind of measure of the relative energy (relative basicity) sensitivity on solvation effect. It is significantly larger in the absolute value for the ΔE(1-2) than for the ΔE(1-3). Due to change of the protonation site (when proceeding from the gas phase to water) the slope of regression line for the ΔE(1-3) has opposite sign to that for the ΔE(1-2). This indicates that investigations on the solute-solvent interactions may clarify the mechanism of histamine activity, particularly the role of the proton-transfer reactions.

Table 6. Parameters of linear regression between the relative energies (ΔE) and macroscopic dielectric function of Kirkwood and Onsager (KO) [a]: $\Delta E = \alpha \cdot KO + \Delta E°$.

ΔE	Conformation	Slope (α)	Intercept (ΔE°)	Correlation coefficient
ΔE(1-2)	*trans*	20.9	–11.6	0.9989
	gauche	29.6	–19.9	0.9996
ΔE(1-3)	*trans*	–11.3	3.6	–0.9999
	gauche	–9.7	3.3	–0.9989

[a] Data taken from Table 3.

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