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Geometry, Energy, and Vibrational Analysis of Taurine and Its Tautomerization in the Aqueous Phase: A DFT Study

Phân tích hình học, năng lượng và dao động của taurine và quá trình tautomer hóa của taurine trong pha nước: Nghiên cứu bằng phương pháp DFT

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Abstract

Taurine is a β-amino acid found in high concentrations within human and animal tissues. It plays critical roles in various metabolic processes, cellular activities, and osmoregulation, and also enhances the solubility and stability of bile acids. In aqueous solution, taurine exists predominantly in its zwitterionic form. This work investigates the geometric structures and thermodynamic aspects of taurine tautomerization in water. We evaluate solvent effects by using an explicit solvation model (i.e., a taurine-water complex), a model that better captures the hydrogen bond network that the implicit model lacks. Our results describe how the tautomerization process is significantly influenced by both the environment and the specific choice of solvent model.

Keywords: Taurine, tautomerization, zwitterion, Density Functional Theory (DFT), aqueous phase, proton transfer

Tóm tắt

Taurine là một axit β-amino được tìm thấy với nồng độ cao trong mô người và động vật. Nó đóng vai trò quan trọng trong nhiều quá trình trao đổi chất, hoạt động tế bào và điều hòa thẩm thấu, đồng thời tăng cường độ hòa tan và độ ổn định của axit mật. Trong dung dịch nước, taurine tồn tại chủ yếu ở dạng lưỡng cực. Nghiên cứu này khảo sát cấu trúc hình học và các khía cạnh nhiệt động học của quá trình tautomer hoá taurine trong nước. Chúng tôi đánh giá ảnh hưởng của dung môi bằng cách sử dụng mô hình solvat hóa tường minh (tức là phức hợp taurine-nước), một mô hình cho phép nắm bắt tốt hơn mạng lưới liên kết hydro mà mô hình ngầm định không thể hiện được. Kết quả chỉ ra rằng quá trình chuyển hóa bị ảnh hưởng đáng kể bởi cả môi trường và sự lựa chọn cụ thể của mô hình dung môi.

Từ khoá: Taurine, tautomer hoá, zwitterion, lý thuyết phiếm hàm mật độ (DFT), pha nước, chuyển proton

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1. Introduction

Taurine (2-aminoethanesulfonic) is a conditionally essential amino acid, containing a sulfonic acid group (SO_3H) instead of a standard carboxylic acid (COOH). It is found in high concentration within the brain, retina, heart, and skeletal muscles in both human and animal bodies. Taurine is not only used to build protein but it also serves as a cellular supervisor, managing critical maintenance tasks. These functions include osmoregulation (maintaining the balance of water and minerals), the formation of bile salts cholesterol breakdown in the liver, the regulation of calcium signaling, and acting as a neurotransmitter, or supporting antioxidant processes [1-3].

In the gas phase (vacuum), taurine prefers to be in neutral (N) form, which is stabilized by an intramolecular hydrogen bond O-H…N between the hydrogen of the sulfonic acid and the nitrogen of the amino group [4]. In contrast, in crystalline, aqueous, or biological environments, it exists almost exclusively as a zwitterion (Zw) [5]. The tautomerization of taurine - the interconversion between these two structural isomers - involves a proton transfer from the acidic sulfonic group to the basic amino group. While previous studies have characterized the zwitterionic forms of conventional amino acids like glycine and alanine in solution [6, 7], research specifically addressing taurine remains sparse. This raises two critical questions: (i) how does the proton transfer mechanism in taurine (SO_3H to NH_2) differ from that in standard carboxylic amino acids (-COOH to NH_2), and (ii) how does an explicit solvation model outperform the implicit model in describing this transition? Notably, implicit methods are often insufficient for accurately modeling the proton transfer mechanism.

In this research, we employ density functional theory (DFT) approach to investigate the structural and thermodynamic aspects of the taurine tautomerism in aqueous environment. We first determine the geometries of taurine in two forms (N and Zw) using an implicit solvent model, followed by the identification of most probable taurine-water complex. By analyzing the transition state (TS), the free energy of activation, as well as the potential energy surface (PES) profile, this work provides new insights into the chemical equilibration of taurine in water.

2. Computational Methods

All calculations were performed using ORCA [8, 9]. Density functional ωB97X-D3 [10,11] with def2-TZVP basis set [12] was used. The long-range corrected ωB97XD functional was recommended because it includes empirical dispersion that can properly treat the system containing the hydrogen bonding and van der Waals interactions, while the def2- TZVP performs better than most of the 6-311G series basis. The implicit Solvation Model based on Density (SMD) was used for implicit description of aqueous phase throughout the work [13]. Vibrational frequency calculation was used to confirm local minima and transition state (one and only imaginary frequency).

3. Results and Discussion

3.1. Optimized structure in water

As taurine (H_2N-CH_2-CH_2-SO_3H) consists primarily of rotatable single bond, its structure is highly flexible. Its conformational space can be defined by five principal backbone torsion angles. Using the GOAT (Global Optimization and Automated Topology) module in ORCA, we generated and optimized 24 local minima and their 24 enantiomers. This conformational scan confirmed that the most stable structure of taurine in water is the zwitterionic (Zw) form.

Figure 1 illustrates the conformers with relative free energy within 1 kcal/mol of the

global minimum, all of which are in the Zw form, alongside the two lowest-energy neutral (N) conformers. A significant energy gap exists between these states; for instance, the two lowest-energy N forms (Cf6N and Cf8N) sit approximately 20 kcal/mol higher than the zwitterionic ground state. The optimized structure of taurine in water ($Cf6_Z$) is stabilized by a strong intramolecular hydrogen bond (1.80 Å) between the hydrogen of amino (NH_3^+) and the oxygen of sulfonate group (SO_3^-). In contrast, the most stable neutral conformer (shown in Figure 2) is 20.64 kcal/mol higher in energy and is stabilized only by a much weaker hydrogen bond (2.34 Å) between the amine hydrogen and a sulfonic oxygen.

The preferred conformer of taurine in gas phase reported by Cortijo *et al*. is stabilized in neutral form, with an intramolecular O-H···N hydrogen bond established between the hydrogen of the sulfonic group and the nitrogen of the amino group [4]. Therefore, the most noticeable water-induced difference in taurine structure involves the change from normal to zwitterionic form.

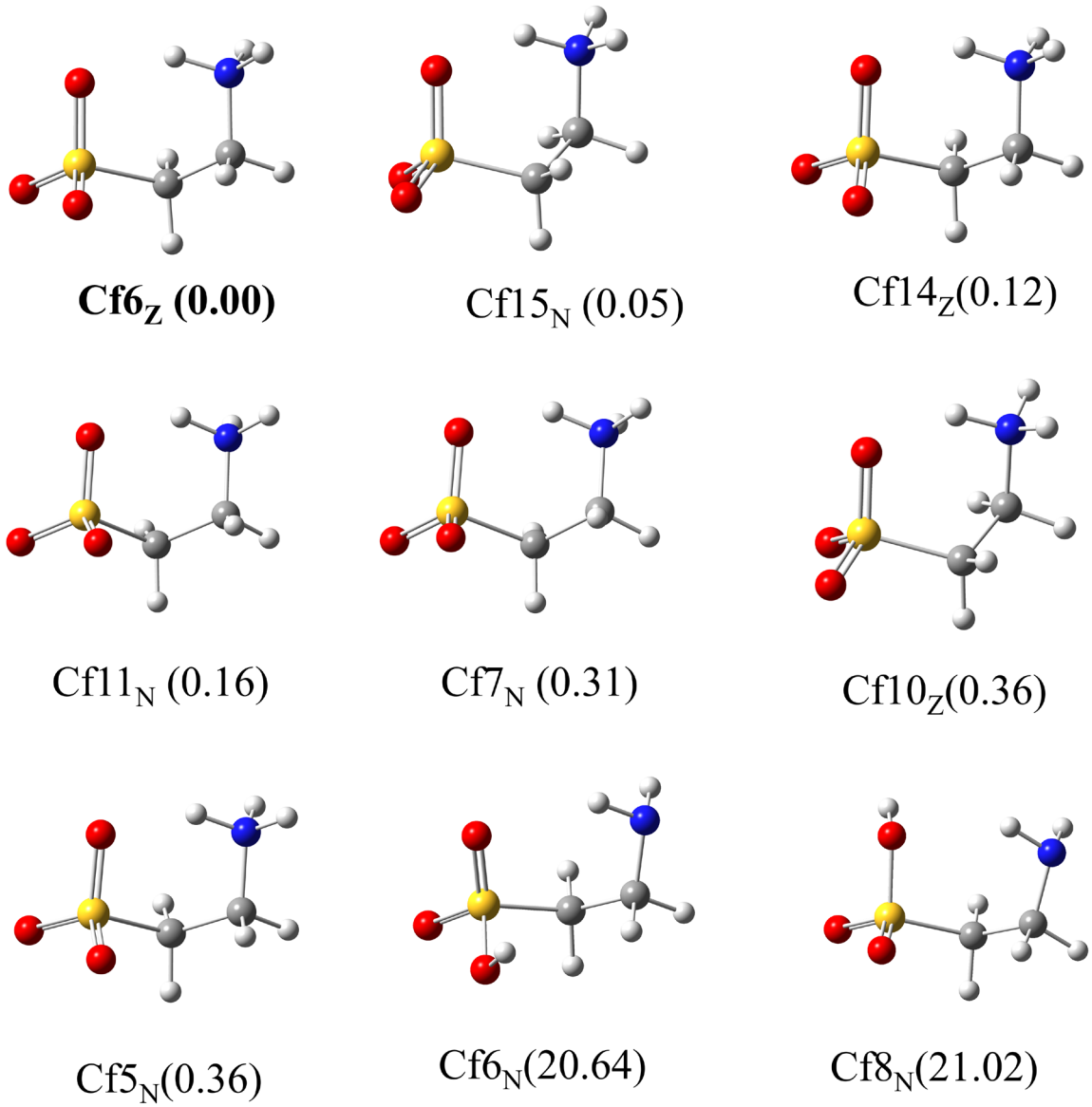


Figure 1. Some of the lowest energy conformers of N- and Zw taurine in aqueous phase (ωB97X-D3/def2-TZVP level of theory). The relative energy of the conformers is given in parentheses (kcal/mol).

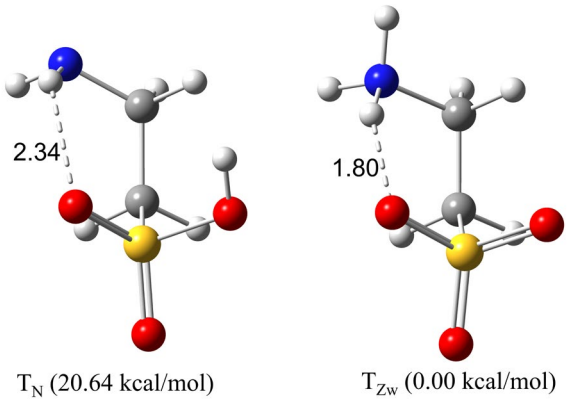


Figure 2. Optimized structures of Taurine in N- and Zw form in aqueous phase (ωB97X-D3/def2-TZVP level of theory). Hydrogen bonds are demonstrated by dash line (Å). The relative energy of the conformers is given in parentheses (kcal/mol).

3.2. Explicit solvation

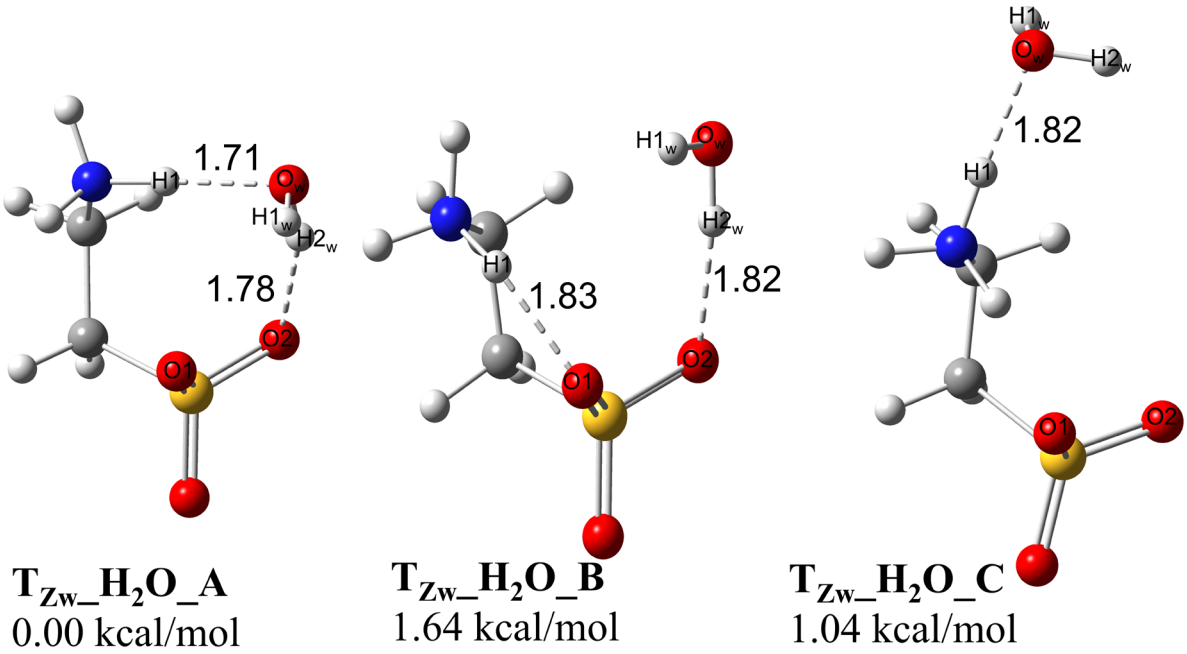


Figure 3. Optimized structures of T_{Zw} form in complexation with a water molecule in aqueous phase (ωB97X-D3/def2-TZVP level of theory). Hydrogen bonds are demonstrated by dash line (Å). The relative energy of the conformers is given in kcal/mol.

The solvation of taurine was further investigated by introducing an explicit water molecule. We explored configurations where the water molecule is positioned near either the sulfonic or amino group, as well as in a "bridge" configuration between these two. The optimized structures and relative energies of these three complexation modes are presented in Figure 3. As a result, T_{Zw}_H_2O_A is identified as the global minimum. In this conformer, the water molecule acts as a bridge, forming hydrogen bonds with both the amino nitrogen and the sulfonic oxygen. Complexation with solely one amino or acid group increases the system energy from 1.04 (T_{Zw}_H_2O_C) to 1.64 kcal/mol (T_{Zw}_H_2O_B), respectively. Moreover, key structural parameters of these complexes, particularly for the connection of the amino and sulfonic acid group with the extra water molecule, are given in Table 1. In the most stable

conformer (T_{Zw}_H_2O_A), the water molecule is stabilized by two hydrogen bonds, i.e., H1···Ow and H2w···O2, with distances of 1.71 and 1.77 Å, respectively. In T_{Zw}_H_2O_B and T_{Zw}_H_2O_C complexes, the water molecules associate with only one functional group at a distance of 1.82 Å. These findings align with previous studies by different groups, which examined taurine conformation in water with implicit (SMD M06-2X/cc-pVTZ) and explicit model with up to four water molecules [5, 14].

Table 1. Key geometric parameters for Taurine-water complex conformers and the relative energy (kcal/mol). Bond distance in Å, angle and dihedral angles in º. Subscript w for the explicit water molecule.

Cf.	**T_{Zw}_H_2O_A**	**T_{Zw}_H_2O_B**	**T_{Zw}_H_2O_C**
N-H1	1.06	1.04	1.03
H1-O1	2.65	1.83	1.86
H1-O_w	1.71	3.34	1.82
$H2_w$-O2	1.77	1.82	-
H1-O_w-$H1_w$	99.9	44.5	-
H1-O_w-$H2_w$	92.0	71.29	-
O_w-$H2_w$-O2	162.7	172.4	-
H1-O_w-$H2_w$-O2	-19.73	47.28	-
H2-O_w	-	-	1.71
N-H2-O_w	-	-	170
H2-O_w-$H1_w$	-	-	104.8
H2-O_w-$H2_w$	-	-	103.6
N-H1-O_w-H1	-	-	-74.2
N-H1-O_w-H2	-	-	33.86

3.3. Tautomerization of taurine in aqueous phase

The tautomerization of taurine in water involves a proton transfer between the amino and sulfonic acid groups. It is well established that for chemical processes involving charged species, such as protons or electrons, the implicit solvent model often fails to provide an accurate free energy value. Consequently, we choose to study the tautomerization of taurine with the water-bridged complex (T_{Zw}_H_2O). Figure 4 shows the PES profile of this reaction, detailing the structural features of its reactant (T_N_H_2O), transition state (TS) and product (T_{Zw}_H_2O). Thermodynamically, the conversion of N to Zw undergoes a transition state located at 1.31 kcal/mol below the reactant (N-form). Although this computed relative energy suggests an extremely facile, potentially barrier-less proton transfer mechanism, this magnitude of energy difference lies within the intrinsic error margin of the employed ωB97X-D3/def2-TZVP functional. Therefore, we suggest that this proton transfer reaction occurs with ultra-low energy barrier. These results align with trends reported for glycine and alanine, although those two amino acids typically exhibit a small positive activation energy of several kcal/mol.

The Zw product is 14.17 kcal/mol more stable than the reactant (N), indicating a highly spontaneous chemical process. In terms of structure, the water molecule in the transition state facilitates the H-transfer by forming an 8-member ring hydrogen bonding network. The TS was confirmed by a single imaginary frequency of -488 cm^{-1}, corresponding to the O1-Hw stretching vibration. The proton from SO_3H group approaches water molecule at a distance of 1.26 Å, while the water molecule maintains an intermediate distance of 1.60 Å from the NH_2 group. Following the proton transfer, it releases the extra proton near the amino group and stabilizes into Zw conformation, with final distances to amino and sulfonic groups being 1.71 and 1.77 Å, respectively.

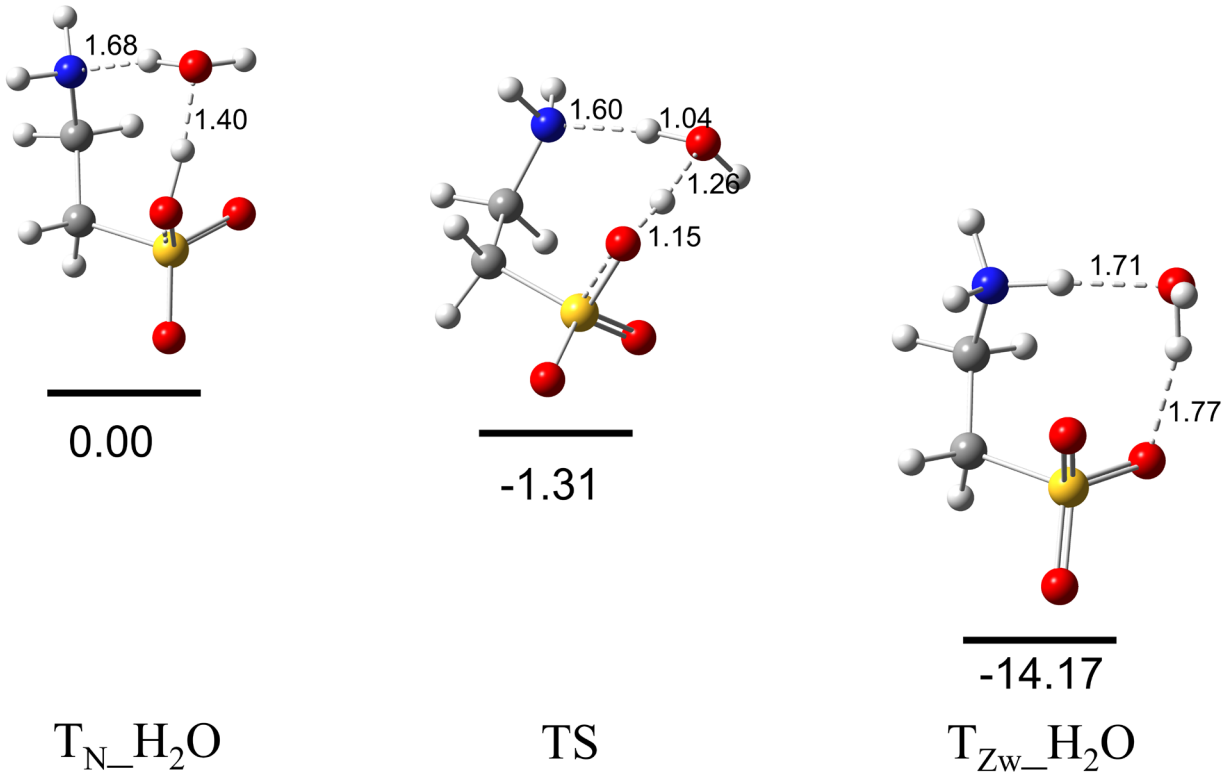


Figure 4. Free energy profile for taurine tautomerism. Energy in kcal/mol.

Finally, we analyzed the vibrational frequency for the reactant (N), TS, and product (Zw) of the taurine tautomerization process. The key vibrational modes for each species are summarized in Table 2. The N-H and O-H stretching modes are the most characteristic features for identifying each state. For example, in the initial N structure, the water-mediated stretching mode (Ow-Hw) are found at 3857 and 2911 cm^{-1}. Upon reaching the transition state, these frequencies shifted to 3845 and 2518 cm^{-1}, respectively. Crucially, the TS is characterized by a single imaginary frequency (at -488 cm^{-1}), which represents the asymmetric stretching of Hw-O1 bond during the proton relay. In the zwitterionic product, the Ow-Hw stretching modes appear at 3873 and 3506 cm^{-1}, accompanied by a prominent N-H1 stretching vibration at 2943 cm^{-1}. These spectral shifts provide clear evidence of a successful and complete proton transfer from the sulfonic O1 atom to the amino nitrogen.

Table 2. Vibrational frequencies (cm^{-1}) of the key bonds for reactant, TS, and product in taurine tautomerization.

Bond vibration	**T_N_H_2O**	**TS**	**T_{Zw}_H_2O**
N-H1			2943 *str.*
O1-H1w	1979 *str.*	-488 *str.*	
Ow-H1w	2911 *str.*	2518 *str.*	3506 *str.*, 3499 *str.*
Ow-H2w	3857 *str.*	3845 *str.*	3873 *str.*
CH2	3188 *rock.*, 3151 *rock.*, 3105 *sci.*, 3078 *sci.*, 1497 *sci.*, 1408 *sci.*	3188 *rock.*, 3155 *rock.*, 3107 *sci.*, 3084 *sci.*, 1409 *sci.*	3209 *rock.*, 3193 *rock.*, 3138 *sci.*, 3115 *sci.*, 1467 *sci.*, 1415 *sci.*
NH2	3607 *rock.*, 3530 *sci.*, 1579 *sci.*	3605 *rock*, 3528 *sci.*, 1574 *sci.*	3499 *sci.*, 1599 *sci.*, 1591 *sci.*, 1504 *sci.*
HwOw	1653 *sci.*	1665 *sci.*, 1534 *sci.*	1647 *sci.*

4. Conclusion

In conclusion, we have investigated the structural and thermodynamic properties of the taurine tautomerization process in aqueous solution using computational method (ωB97X-D3/def2-TZVP level of theory). Our results confirm, in agreement with existing literature, that taurine exists predominantly in its zwitterionic form in water. Specifically, the stabilization is achieved through complexation with an explicit solvent molecule (water) that acts as a proton bridge. This water-assisted tautomerization is highly spontaneous (-14.17 kcal/mol) and proceeds *via* a very-low-activation-energy mechanism. These findings provide critical insights into the molecular behavior of taurine in aqueous environments and serve as a foundation for further exploring its diverse biological functions.

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