Unveiling the tautomerism of sulfapyridine: Solvent effects on stability and ultraviolet/visible UV absorption spectra

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Abstract
Here, a theoretical investigation based on Density Functional Theory is carried out about the effects of microsolvation on the tautomerization mechanism and absorption ultraviolet/visible (UV/Vis) spectrum of sulfapyridine (SPY). First, the interconversion barriers of SPY (a sulfonamide) to its tautomer (sulfonimide) are probed. Hence, explicit solvation decreases this barrier height and induces a more spontaneous tautomer formation in aqueous solution. The similarity between the UV/Vis spectrum of this tautomer and the experimental one is another evidence that this tautomeric equilibrium cannot be ignored.

Introduction
Tautomerism is a fundamental chemical phenomenon among interconvertible compounds, known as tautomers, which coexist in dynamic equilibrium [1]. The solvent polarity can have a significant impact on the stability and distribution of tautomers in solution. This can influence the efficacy of processes such as the photodegradation of environmental contaminants and the bioavailability of drugs [2]. In addition, protic solvents, such as water and alcohols, can facilitate proton transfers, affecting the interconversion rates between tautomers and, consequently, their chemical properties [1,2].

Different tautomers can exhibit distinct absorption spectra due to variations in the electronic distribution and structures of the molecules [1,2]. These differences can be used to identify and quantify tautomers in solutions and mixtures, offering valuable insights into the composition and behavior of the compounds studied [1,2].

Thus, in the present work, a theoretical investigation is performed regarding the effect of microsolvation on the interconversion mechanism and stability of sulfapyridine (SPY) regarding its tautomeric form (TAUT) in aqueous solution, which are illustrated in Fig. 1. In addition, the ultraviolet/visible (UV/Vis) absorption spectra in gas phase, as well as in solutions with water and ethanol, are also reported.

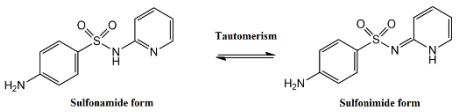

Fig. 1 – SPY tautomerization mechanism.

Methodology
Geometry optimizations and vibrational frequency calculations were performed at the PBE-D3(0)/cc-pVTZ level of theory in gas phase, as well as in solutions with water and ethanol, using the polarizable continuum model (PCM) [3]. Up to two explicit water molecules were also included in some of these calculations, which are carried out within Gaussian09 [4] package.

Next, to improve the stability description of SPY and TAUT in aqueous solutions, ONION (QM/XTB2) calculations were performed to include the explicit solvent. The quantum mechanical (QM) region, defined as the 28 atoms composing the SPY and TAUT structures, which were treated by using PBE-D3(BJ)/DEF2-TZVP with DEF2/J [5] auxiliary basis sets, while solvent effects were included with the Semiempirical Extended Tight-Binding Program Package (XTB2) [6] and the ALPB

[7] implicit solvent model. Geometry optimization and vibrational frequency calculations are done with this protocol. The initial structures for the clusters containing 43 water molecules were extracted from molecular dynamics (MD) calculations using the Autosolvate software [8].

Time dependent density functional theory (TD-DFT) with and without the Tamm-Dancoff approximation (TDA) were carried out with the CAM-B3LYP/DEF2-TZVP [9] level, along with DEF2/J auxiliary basis sets, to obtain the UV/Vis spectra of SPY and TAUT. These calculations were carried out in gas-phase and in solutions with water and ethanol, with the conductor-like polarizable continuum model (C-PCM) [10]. The number of states requested was 30 for singlet and 30 for triplet excitations. Onion, TD-DFT and TDA-DFT calculations were performed within the ORCA 5.04 package [11].

A temperature of 298.15 K was considered to thermodynamic properties.

Results and Discussion

First, the interconversion barriers for the SPY tautomerism mechanism in aqueous solution are presented in Fig. 2.

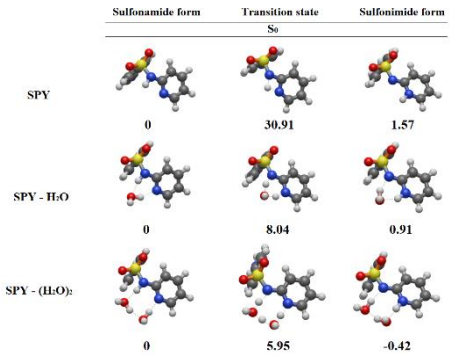

Fig. 2 - Equilibrium structures and relative Gibbs energies for the sulfapyridine tautomeric forms and the TS for the interconversion process (in kcal mol^{-1}).

Thus, the Gibbs activation energy decreases from 30.91 kcal.mol^{-1} with only implicit solvation (PCM) to 8.04 and 5.95 kcal.mol^{-1}, respectively, with the inclusion of one and two explicit water molecules. Furthermore, the formation of the tautomeric form is now spontaneous with two water molecules (-0.42 kcal.mol^{-1}). This indicates that the interconversion of SPY (sulfonamide) to its tautomeric form (sulfonimide) should occur much faster at room temperature as long as interactions with explicit solvent molecules are properly considered. In Fig. 3, the relative Gibbs energies obtained from ONIOM (QM/XTB2) calculations are illustrated. Now, the tautomeric formation becomes even more spontaneous along the increase of explicit solvent molecules, -8.60 kcal.mol^{-1}. Thus, it is possible to predict that the tautomeric form of SPY predominates in aqueous solutions at room temperature.

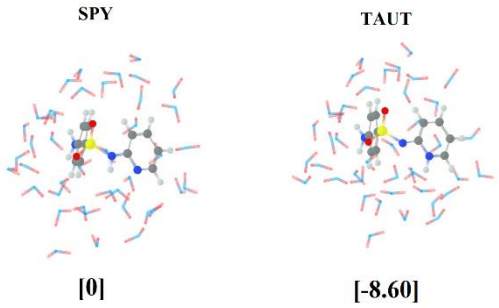

Figure 3 - Equilibrium structures and relative Gibbs energies for the sulfapyridine tautomeric forms obtained from ONIOM (QM/XTB2) with ALPB implicit solvation (in kcal mol $^{-1}$).

In the sequence, Fig 4. shows the UV/Vis absorption spectra for SPY and TAUT in gas-phase, as well as in solutions with water and ethanol. For comparison purposes, the TDA approach was also used in this work. Overall, TDA results in a blueshift in all spectra as compared to traditional TD-DFT data. In addition, the generalized oscillator strengths (GOSs) exhibit an increase of up to 60%. Solvent effects also led to band shifts and in an increase in GOSs, although the effect of the two different solvents on the spectra was practically identical. Although we did not find a complete spectrum of SPY in water, Velraj *et al.* (2014) obtained an experimental spectrum of SPY in ethanol, where the absorption bands observed are centered at 282, 258 and 211 nm [12]. Interestingly, the UV/Vis spectrum obtained for TAUT with the TDA approximation provides the closest accordance with the experiment, with absorption bands centered at 281, 240 and 219 nm in the region covered by the experimental apparatus. This seems to be a major evidence that the tautomer structure is the predominant form for this compound in ethanol.

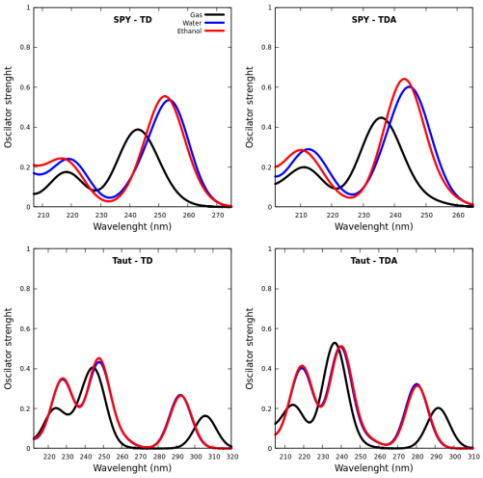

Fig. 4 - UV/Vis absorption spectra for SPY and TAUT obtained in gas-phase, water and ethanol.

Conclusions

In summary, we investigate the effects of microsolvation on the tautomerization mechanism and the UV/Vis absorption spectra of SPY (sulfonamide). The results obtained indicate that the interconversion is fast and the tautomeric form (sulfonimide) should be predominant in aqueous solution at room temperature. The absorption band around 290 nm, characteristic of the tautomeric form, was found in an experimental spectrum of SPY. This is evidence that the tautomeric equilibrium of SPY should be considered in studies concerning the biological activity or photodegradation mechanisms of SPY in protic solvents.

Acknowledgements

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References

1. Antonov L, editor. Tautomerism: methods and theories. John Wiley & Sons; 2013.
2. Powling J, Bernstein HJ. The effect of solvents on tautomeric equilibria. Journal of the American Chemical Society. 1951 Sep;73(9):4353-6.
3. Mennucci B. Polarizable continuum model. Wiley Interdisciplinary Reviews: Computational Molecular Science. 2012;386-404.
4. M.J. Frisch et al., Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT, 2013.
5. Weigend F, Ahlrichs R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. Physical Chemistry Chemical Physics. 2005; 3297-305.
6. Bannwarth C, Ehlert S, Grimme S. GFN2-xTB—An accurate and broadly parametrized self-consistent tight-binding quantum chemical method with multipole electrostatics and density-dependent dispersion contributions. Journal of chemical theory and computation. 2019:1652-71.
7. Ehlert S, Stahn M, Spicher S, Grimme S. Robust and efficient implicit solvation model for fast semiempirical methods. Journal of Chemical Theory and Computation. 2021;4250-61.
8. Hruska E, Gale A, Huang X, Liu F. AutoSolvate: A toolkit for automating quantum chemistry design and discovery of solvated molecules. The Journal of Chemical Physics. 2022.
9. Yanai T., Tew D. P. , Handy NC. A new hybrid exchange–correlation functional using the Coulomb-attenuating method (CAM-B3LYP). Chemical physics letters. 2004,51-7.
10. Cossi M, Rega N, Scalmani G, Barone V. Energies, structures, and electronic properties of molecules in solution with the C-PCM solvation model. Journal of computational chemistry. 2003, 669-81.
11 Neese F. The ORCA program system. Wiley Interdisciplinary Reviews: Computational Molecular Science. 2012.
12. Velraj G, Soundharam S. Structure, vibrational, electronic, NBO and NMR analyses of 4-amino-N-[2-pyridinyl] benzene sulfonamide (sulfapyridine) by experimental and theoretical approach. Journal of Molecular Structure. 2014, 475-86.