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Theoretical investigation of the implicit effects water molecules and resonance interactions on structural stability and NMR tensors of hallucinogenic harmine by density functional calculations

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ABSTRACT

Density functional theory (DFT) was used to investigate the effects of intra-molecular interactions and implicit water molecules on the relative stability and the NMR shielding tensors of hallucinogenic harmine in the monomeric and dimeric states. Results represented that the relative stability and the NMR shielding tensors are dependent on the resonance interactions and chemical environment. However, their values are obviously different in the considered states and the media. The energetic data demonstrated that dimeric and monomeric states of harmine in water medium are more stable than they are in the gaseous form. Based on NBO interpretation and NMR calculations, it can also be concluded that by increasing lone pair electrons contribution of nitrogen atoms in resonance interactions and aromaticity development in the monomeric – dimeric states, the values of NMR chemical shielding around them increase.

Keywords: Harmine; NMR chemical shielding; NBO interpretation; monomer; dimer

INTRODUCTION

β-Carboline derivatives (H-pyrido [3, 4-b] indol derivatives) (BC) make up a group of drug-binding alkaloids, widely distributed in nature. Harmine [$C_{13}H_{12}N_2O$] (MeO-1-1Me-9H-7pyrido [3,4-b]-indole) is a well known member of the β-caroline alkaloid family (see, Fig. 1). They have interesting biological and photophysical properties such as hypotensive, hallucinogenic or antimicrobial actions and tremorogenesis. Researchers demonstrated that harmine and other β-Carbolines interfere the action of reactive oxygen species, protecting the nervous system. This behavior is due to their antioxidative properties [1-3]. Harmine is a well known member of the β-caroline alkaloid family. β-Carboline belongs to the class of indole alkaloids and consists of the pyridine ring fused to the indole skeleton. They are available in a broad range of medicinal plants and are endogenously produced in human and animal tissues as a product of secondary metabolism [4-7]. They have different biological properties such as hypotensive, hallucinogenic or antimicrobial activities

[8]. The analysis of β-Carboline alkaloids can be carried out by HPLC with fluorimetric UV-Vis spectrophotometric

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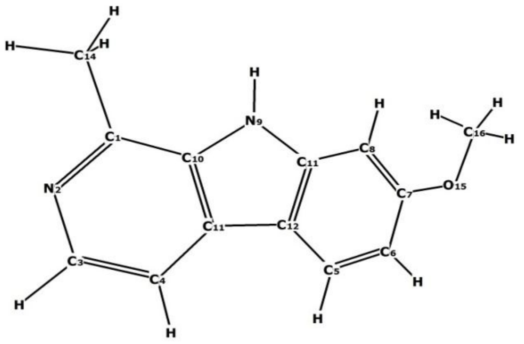
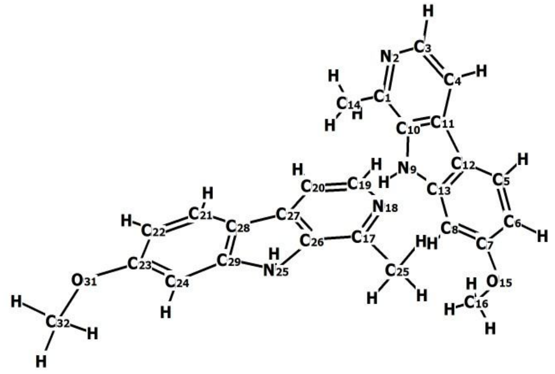
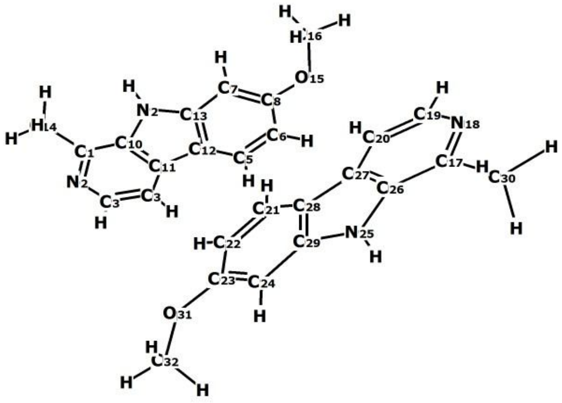
*Corresponding author: nedaahmadinejad8810@yahoo.com and mass spectrometry detection [9, 10]. Since harmine can be a metabolite of harmane, their separation is very important. However, the application of conventional HPLC techniques to this separation is often difficult and micellar electrokinetic chromatography has been proposed as an alternative. Natural and chemically modified cyclodextrins (CDs) have been profusely used to increase the resolution of chromatographic techniques and capillary electrophoresis. On the other hand, CDs provide an enhancement of the sensitivity in the luminescence methods for the detection of fluorophores [11-13]. As we know, pharmacological activities are performed in water medium. However, recognition of structure and how intra-molecular interactions is very important in this phase. In this paper, we studied the effect of implicit water molecules on the relative stability of monomeric and dimeric states. The basic interest of the present research is to analyze the effects of structural interactions in the water media on the relative stability and NMR chemical shielding using density functional theory (DFT) and the polarizable continuum model (PCM) in the water media and NBO interpretation.



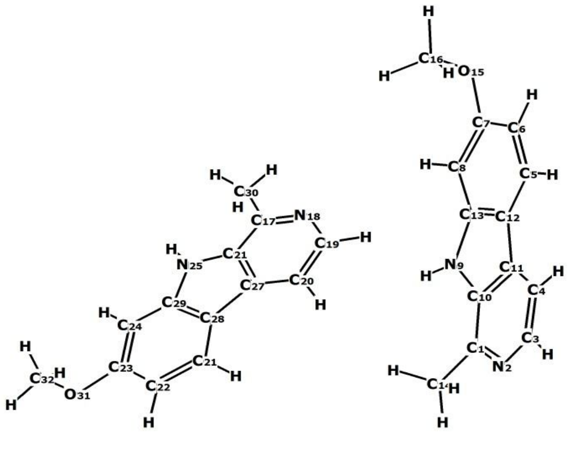
a)monomer



b) Dimer 1



Dimer 2



Dimer 3

Fig. 1. Optimized structures of (amonomer and b) Possible states of dimer from the Harmine crystallographic structure.

COMPUTATIONAL METHODS

The monomeric and the Possible three states of the dimeric structures from crystallographic structure have been optimized at the B3LYP/6-311++G** and B3LYP/6-311G** levels of theory in water and gaseous phases. Bulk effects were modeled on the interested structures by Self-Consistent Reaction Field (SCRF) method which is based on a continuum model with uniform dielectric constant (ε). Tomasi's Polarized Continuum Model (PCM) defines the cavity as a union of a series of interlocking atomic spheres [14]. NBO analysis and GIAO nuclear magnetic shielding calculations were then performed at the B3LYP/6-311++G** level of theory on the optimized monomeric structure and the most stable dimeric state in the gaseous and solution phases [15-17].The values of symmetric shielding (Δσ) and asymmetry shielding (η) were calculated by below formulas [18, 19]:

1) The isotropic value σ_{iso}:

$\sigma_{iso} = 1/3(\sigma_{11}+\sigma_{22}+\sigma_{33})$(1)

2) The anisotropy shielding (Δσ)

$\Delta\sigma = \sigma_{33}-1/2\ (\sigma_{11}+\sigma_{22})$(2)

And

3) The asymmetry parameter (η) :

$$\eta = \frac{|\sigma_{22} - \sigma_{11}|}{|\sigma_{33} - \sigma_{iso}|} \quad (3)$$

All of the calculations have been performed with the Gaussian 03 package of programs [20].

RESULTS AND DISCUSSION

Energy results

The relative energy values (ΔE_{rel}) of the Harmine structure were reported in Table 1 at different levels of the theory in the gas and water phases. The relative energies values of Harmine monomeric and dimeric structures were reported in the gaseous and water media. Results showed that the relative stability of the first dimeric state (dimer 1) is more than those of other dimeric states. Furthermore, the relative stability in water medium is more than it is in gaseous former for both considered states. On the other hand, the comparison of ΔE_{rel} values in the different medium and gaseous form shows that the relative stability was observed more obviously at the water medium than at the gaseous state (in the monomer and dimer 1).

Table1. Calculated Relative Energy Values (kca.mol^{-1})for dimeric and monomeric structures of Harmine in the different levels of theory and media

Structure	**Method**	**E_{el}**	**ΔE_{el}**
	Water		
Monomer	6 - 311++G(d‹p)	-687.5459	0.0000
	Gaseous		
	6- 311++G(d‹p)	-687.5277	11.4207
	Water		
Dimer 1	6- 311G(d‹p)	-1375.0697	0.0000
	Gaseous		
Dimer 1	6- 311G(d‹p)	-1375.0493	12.8012
Dimer 2	6-311G(d, p)	-1375.0374	-
Dimer 3	6- 311G(d‹p)	-1375.0342	-

NBO analysis

The NBO interpretation indicates that the resonance energy for LP(N9) → σ* and π* interactions of the structural pyrrole ring increases while the LP(N9) occupancy decreases, and the highest value of the resonance energy and the lowest occupancy were observed in water medium. These findings are in good agreement with the energy data and they can be the probable structural reasons for the harmine stability in water medium. In addition, the resonance interactions for LP N→ σ* or π* delocalizations and LP Ns occupancies in water phase are more and less than they are for gaseous former in both dimeric and monomeric states, respectively (See Table 2).

Table 2. Calculated lone pair and bonding orbital occupancies, natural charges and resonance energies (in kcal mol^{-1}) for involved atoms and bonds in dimeric and monomeric structures of Harmine using NBO analysis at the B3LYP/6-311++G** level

Structure	**Solvent**	**Donor NBO**	**Occupancy**	**Charge**	**Acceptor NBO**	**Resonance energy (kcal/mol)**	
Monomer	**Gaseous**	LP (1) N_2	1.91565	-0.47150	BD*(1) C_1-C_{10} BD*(1) C_1-C_{14} BD*(1) C_3-C_4 BD*(1) C_3-H_{17} BD*(1) N_9-C_{10}	9.72 2.37 8.94 3.94 0.53	25.50
		LP (1) N_9	1.66709	-0.55478	BD*(2) C_{10}- C_{11} BD*(2) C_{12}- C_{13}	31.93 36.22	68.15
	Water	LP (1) N_2	1.92231	-0.52462	BD*(1) C_1-C_{10} BD*(1) C_1-C_{14} BD*(1) C_3-C_4 BD*(1) C_3-H_{17} BD*(1) N_9-C_{10}	9.45 2.23 8.75 3.67 0.51	24.61
		LP (1) N_9	1.63996	-0.55715	BD*(2) C10- C11 BD*(2) C12- C13	35.54 39.31	74.85
Dimer	**Gaseous**	LP (1) N_2	1.91497	-0.47695	BD*(1) C_1-C_{10} BD*(1) C_1-C_{14} BD*(1) C_3-C_4 BD*(1) C_3-H_{33} BD*(1) N_9-C_{10}	9.63 2.35 8.86 3.98 0.50	25.32
		LP (1) N_9	1.63458	-0.58214	BD*(2) C10- C11 BD*(2) C12- C13	35.17 40.12	75.29
		LP (1) N_{18}	1.89422	-0.53262	BD*(1) C_{17}-C_{26} BD*(1) C_{17}-C_{30} BD*(1) C_{19}-C_{20} BD*(1) C_{19}-H_{45} BD*(1) N_{25}-C_{26}	7.54 2.78 8.13 4.17 0.51	21.13
		LP (1) N_{25}	1.66402	-0.55475	BD*(2) C26- C27 BD*(2) C28- C29	32.53 36.25	68.78
	Water	LP (1) N_2	1.91895	-0.51689	BD*(1) C_1-C_{10} BD*(1) C_1-C_{14} BD*(1) C_3-C_4 BD*(1) C_3-H_{33}	10.48 2.33 9.10 4.27	26.18
		LP (1) N_9	1.62110	-0.57406	BD*(2) C10- C11 BD*(2) C12- C13	37.68 42.14	79.82
		LP (1) N_{18}	1.88756	-0.54791	BD*(1) C_{17}-C_{26} BD*(1) C_{17}-C_{30} BD*(1) C_{19}-C_{20} BD*(1) C_{19}-H_{45} BD*(1) N_{25}-C_{26}	9.61 2.42 8.17 4.36 0.50	25.06
		LP (1) N_{25}	1.64436	-0.54569	BD*(2) C26- C27 BD*(2) C28- C29	35.35 39.04	74.39

NMR chemical tensors. NMR chemical shifts

In this study, the effects of implicit water molecules and intra-molecular interactions on the ^{15}N NMR shielding tensors of dimeric and monomeric harmineat the B3LYP/6-311++G** level of theory have also presented (see Table 3). The obtained results showed that ^{15}N NMR shielding tensors are strongly affected by chemical environment and resonance interactions. Table of data represented that nitrogen of pyrrole ring has more value of chemical shielding (σ_{iso}) than nitrogen of pyridine ring in both dimeric and monomeric states in the considered media. NBO analysis also showed that the lone pair of electrons of pyrrole ring' nitrogen have lower occupancy and higher resonance energy for LP N→ σ* or π* delocalizations thanpyridine ring' nitrogen. The obtained results indicated that by the passing of monomeric to dimeric structure, that nitrogens of pyrrole rings have higher value of isotropic chemical shielding (σ_{iso}) and more negative charge than nitrogens of pyridine rings. On the other hand, the NBO data showed that their occupancies decrease and their charges increase. Furthermore, resonance energy for LP N_9→ σ* or π* and LP N_2→ σ* or π* delocalizations in dimeric state is more and less than they are in monomeric former.

CONCLUSIONS

This work provides a reasonable scheme from the effects of intra-molecular interactions and chemical medium on the electronic structure. The results represented that:

- The relative stability of Harmine dimeric and monomeric structures is dependent on resonance interactions and chemical medium. So that, the most stable structure of dimeric and monomeric Harmine is observed in aqueous solution.

-Intra-molecular interactions are controlled by solvent chemical medium. On the other hand, they control ^{15}N chemical shielding tensors in dimeric and monomeric structures of Harmine.

- By the passing of the gaseous to water phase and monomeric to dimeric states, it is observed lone pair electrons contribution of pyrrole ring' nitrogen (N_9) in resonance interactions and aromaticity development increases. however, the values of NMR chemical shielding around them increase.

Table 3. NMR parameters of ^{15}Nnuclei (isotropic, σ_{iso}, anisotropic, $\Delta\sigma_{iso}$, and asymmetric, η, chemical shielding (in ppm)) involving in harmine structure at the B3LYP/6-311++G** level of theory in the gaseous and water phases

Compounds	**Solvent**	Nuclei	σ_{iso}	$\Delta\sigma_{iso}$	η
monomer	**Gaseous**	N2	-83.9488	508.3875	0.4933
		N9	131.6290	39.8322	2.3954
	Water	N2	-178.0195	374.3012	0.8035
		N9	123.1643	90.4707	1.3839
Dimer	**Gaseous**	N2	-84.1093	513.3193	0.5436
		N9	118.6888	72.2881	0.7295
		N18	-61.5380	-336.3344	1.6378
		N25	132.3630	-71.0239	1.6378
	Water	N2	-72.4764	497.7234	0.4983
		N9	113.5670	83.1775	0.5447
		N18	-56.1457	-324.6266	1.8171
		N25	127.5281	-75.5704	0.4487

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