

Theoretical Studies of the Vibrational Spectra of Doxepin

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Absrtact:-

Doxepin is tricyclic antidepressants. Perdew and Wang (GGA-PW91) and Becke-Lee-Yang-Parr (GGA-BLYP) developed the Generalized Gradient Approximation methods which is useful in studying the parameters like molecular geometries, harmonic vibrational frequencies, quantum chemical parameters and thermodynamic properties of doxepin. The BLYP/PW91 analyses of the wave numbers show that the frequencies assigned to doxepin are higher in the gas phase and solution media. Doxepin has been studied mainly by [4-13,15,16].

. **Keywords:** Doxepin, Infrared (IR) spectra, Quantum chemical parameters

Introduction

Doxepin [3-dibenzo (b,e) oxepin-(6H)-ylidene-N,N- dimethyl-1-propanamine] is tricyclic antidepressant (TCAs). It has a tertiary amine chemical structure and have been used for the treatment of depression and anxiety disorders [1]. The synthesis Doxepin hydrochloride by Grignard Reactions in Toluene was reported by Jalander, L [2]. The absorption and fluorescence spectra of doxepin in solvents with different polarities and in β -cyclodextrin have been recorded by Sankaranarayanan *et al.* [3]. They analyzed the solid inclusion complexes of drug by Fourier Transform Infrared (FT-IR) spectra. The understanding of chemical and biological properties of compounds depends largely on knowledge of their molecular structures and spectral behaviors. This work describes the structural and vibrational properties of the doxepin. The purpose of this work is a detailed investigation of the vibrational spectra of doxepin.

Geometric Structure

The structures and the optimized configurations of doxepin is presented in Fig. 1. Table 1 shows the bond lengths and the bond angles of this drugs in accordance with the atom numbering schemes of the molecules as presented in Fig. 1. According to our calculations, the bond lengths and the bond angles of this drug in gas phase is approximately equal to their corresponding bond lengths and bond angles in their solution media. The differences between the doxepin O-C8-C9 and O-C5-C4 bond angles in the gas phase

and their corresponding values in solution media (0.346, 0.368 degrees) is observed quite high.

CH₃ vibrations.

Two methyl groups are present doxepin which are directly connected to the nitrogen atom. For methyl groups, the asymmetric stretching vibrations are observed in the region 2950-3080 cm⁻¹ and the symmetric stretching appears in the region 2900-2970 cm⁻¹ [14].

The BLYP/PW91 calculations assign the ranges of asymmetric stretching vibrations of the methyl groups of doxepin to be 3017-3065 cm⁻¹ and 3044-3100 cm⁻¹ in the gas phase and 3013-3067 cm⁻¹ and 3029-3103 cm⁻¹ in solution media. The BLYP calculations assign values of symmetric stretching bands to be 2865, 2850 and 2836 cm⁻¹ in the gas phase and 2860, 2864 and 2872 cm⁻¹ in solution media. However, the PW91 method assigns values of symmetric stretching bands to be 2884, 2872 and 2853 cm⁻¹ in the gas phase and 2894, 2887 and 2861 cm⁻¹ in solution media. The doxepin asymmetrical deformation modes have been determined in the ranges 1443-1491 cm⁻¹ (BLYP) and 1446-1482 cm⁻¹ (PW91) for gas phase and in the ranges 1442-1478 cm⁻¹ (BLYP) and 1442-1482 cm⁻¹ (PW91) for solution media. For this molecule, the BLYP/PW91 calculated values of symmetric deformation modes are 1416 cm⁻¹ and 1433, 1432 and 1402 cm⁻¹ in the gas phase and 1408, 1432 cm⁻¹ and 1400, 1426 and 1420 cm⁻¹ in solution media

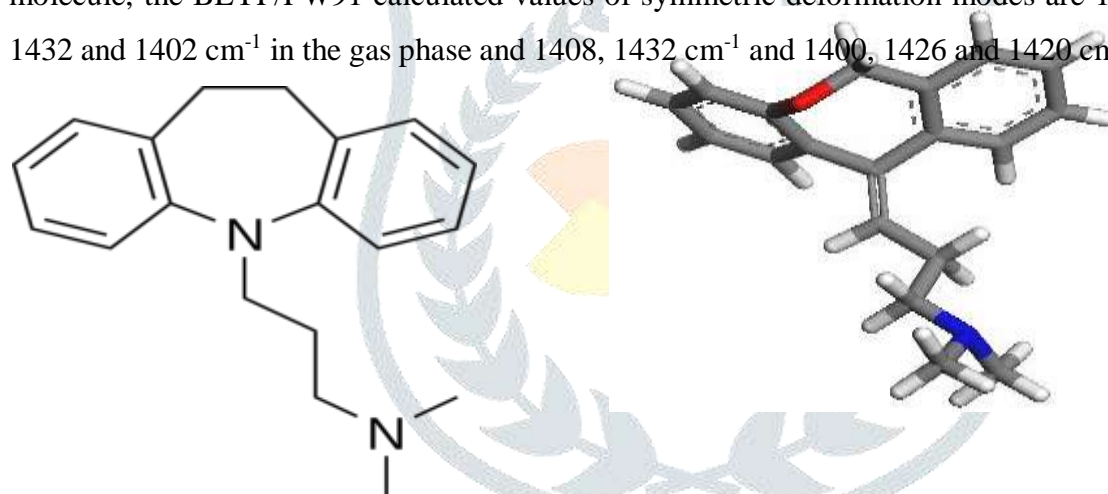


Fig. 1. The structures and the Optimized geometries (BLYP) of doxepin

Ring vibrations.

The C-H stretching vibrations of aromatic structures generally occur in the region 3050-3150 cm⁻¹. The regions of C-H stretching vibrations of the R1 and R3 rings of doxepin have been assigned to be 3102- 3150 cm⁻¹ by BLYP method and 3137-3182 cm⁻¹ by PW91 method in the gas phase and same regions have been assigned to be 3122-3152 cm⁻¹ by BLYP method and 3147- 3184 cm⁻¹ by PW91 method in solution media.

Table 1. Bond Lengths and Bond Angles Doxepin Optimized by BLYP and PW91

	BLYP	PW91	BLYP	PW91
C1-C2	1.400	1.396	1.401	1.397
C2-C3	1.401	1.396	1.402	1.397
C3-C4	1.406	1.401	1.408	1.402
C4-C5	1.408	1.403	1.408	1.404
C5-C6	1.398	1.393	1.398	1.393
C1-C6	1.401	1.396	1.402	1.397
C6-H19	1.088	1.089	1.089	1.089
C1-H16	1.089	1.089	1.089	1.089
C2-H17	1.089	1.089	1.089	1.089
C3-H18	1.089	1.090	1.089	1.090
C5-O	1.398	1.386	1.401	1.389
C5-S	-	-	-	-
C8-O	1.445	1.430	1.452	1.437
C8-S	-	-	-	-
C8-C9	1.528	1.516	1.527	1.515
C9-C10	1.417	1.412	1.419	1.414
C10-C11	1.496	1.486	1.499	1.489
C4-C11	1.497	1.487	1.498	1.488
C8-H20	1.097	1.097	1.096	1.097
C8-H21	1.104	1.104	1.101	1.102
C10-C12	1.415	1.410	1.416	1.411
C12-C13	1.395	1.391	1.396	1.392
C13-C14	1.400	1.395	1.401	1.397
C14-C15	1.396	1.391	1.397	1.392
C9-C15	1.407	1.402	1.408	1.403
C15-H25	1.091	1.092	1.090	1.091

For the doxepin, the bands at 1479-1613 cm^{-1} (also 1300 cm^{-1}) (BLYP) and 1485-1646 cm^{-1} (also 1323, 1327 cm^{-1}) (PW91) are assigned to ring carbon- carbon stretching vibrations in the gas phase and vibrations bands found at 1470-1616 cm^{-1} (also 1298 cm^{-1}) (BLYP) and 1558-1641 cm^{-1} (also 1320, 1332 cm^{-1}) (PW91) are assigned to ring carbon-carbon stretching vibrations in solution media.

CH₂ vibrations.

For the doxepin, these vibrations were calculated 2948, 3033 cm^{-1} in the gas phase and 2969, 3046 cm^{-1} in The dosulepin CH₂ group (H32-C31-H33) asymmetric stretching vibration modes were calculated 3029, 3002 cm^{-1} (BLYP) and 3039, 3013 cm^{-1} (PW91) in the gas phase and 3031, 2998 cm^{-1} (BLYP) and 3043, 3003 cm^{-1} (PW91) in solution media. For the doxepin, these vibrations were assigned to be 2836-

3049 cm^{-1} in the gas phase and 2860- 3039 cm^{-1} in solution media by BLYP method and 2853- 3071 cm^{-1} in the gas phase and 2860-3057 cm^{-1} by PW91 method in solution media.

For the doxepin, these modes have been calculated to occur at 2963 cm^{-1} (BLYP) and 2976 cm^{-1} (PW91) in the gas phase and 2964 cm^{-1} (BLYP) and 2975 cm^{-1} (PW91) in solution media.

The asymmetric stretching vibration modes of CH_2 group (H29-C28-H30) are less than CH_2 group (H32-C31- H33) modes. These modes have been calculated 3029 cm^{-1} (BLYP) and 3039 cm^{-1} (PW91) in the gas phase and 3031 cm^{-1} (BLYP) and 3043 cm^{-1} (PW91) in solution media. For the doxepin, these vibrations are assigned to occur at 3049 cm^{-1} in the gas phase and 3039 cm^{-1} in solution media by BLYP method and 3071 cm^{-1} in the gas phase and 3056 cm^{-1} in solution media by PW91 method.

C-S vibrations

The band due to C-S stretching vibrations is observed in the region 245-1035 cm^{-1} [16]. The BLYP/PW91 method shows C-S vibrations are found at 524 cm^{-1} and 529 cm^{-1} in the gas phase and at 528 cm^{-1} and 524 cm^{-1} in solution media.

C-O vibrations

The C-O stretching vibrations were calculated in the range 981-1219 cm^{-1} by BLYP method and in the range 1022-1237 cm^{-1} by PW91 method in gas phase and in the range 971-1217 cm^{-1} by BLYP method and in the range 1007-1196 cm^{-1} by PW91 method in solution media. The C-O bands occur in the region 1000-1300 cm^{-1} in literature [17].

C-N vibrations

The doxepin, C-N stretching mode is calculated in the range 820-1032 cm^{-1} and 841-1032 cm^{-1} in the gas phase and 819-1024 cm^{-1} and 834-1027 cm^{-1} in the solution media By BLYP and PW91 methods. The C-S group has less polarity than C-O and C-N groups and has considerably weaker bands. Besides the stretching vibrations, the C-O, C-S and C-N groups give rise to twisting and wagging vibrations.

Thermodynamic Properties

Thermodynamic properties are used to describe the effects of temperature on structural stabilities of materials.

Entropy (S), heat capacity (C_p), enthalpy (H) and Gibbs free energy (G) doxepin were calculated at different temperatures in both gas and solution media.

Table 2. Calculated Fukui Functions for Nucleophilic Agents

Gas

Solvent

	BLYP	PW91	BLYP	PW91
C1	0.008	0.009	0.004	0.006
C2	0.004	0.004	0.001	0.003
C3	0.002	0.001	0.002	0.004
C4	-0.012	-0.013	-0.001	-0.002
C5	0.002	0.001	0.006	0.004
C6	0.005	0.005	0.001	0.004
O	-0.003	-0.001	0.002	0.002
S	-	-	-	-
C8	-0.006	-0.006	0.000	-0.001
C9	0.005	0.005	0.007	0.006
C10	-0.012	-0.013	0.001	0.000
C11	0.039	0.040	0.015	0.019
C12	-0.008	-0.008	0.000	0.000
C13	0.002	0.002	0.003	0.003
C14	0.009	0.010	0.004	0.007
C15	0.005	0.005	0.002	0.004
C26	-0.024	-0.026	-0.001	0.002
C28	-0.023	-0.022	-0.020	-0.021
C31	-0.057	-0.057	-0.042	-0.039
N34	0.197	0.198	0.250	0.238
C35	-0.054	-0.052	-0.029	-0.028
C39	-0.056	-0.054	-0.030	-0.028

Quantum Chemical Parameters

Using the optimized geometries, the energy of the highest occupied molecular orbital (E_{HOMO}), the energy of the lowest unoccupied molecular orbital (E_{LUMO}), the energy gap (ΔE), the ionization potential (IP), the electron affinity (EA), the global hardness (η), the global softness (σ), the chemical potential (χ), the dipole moment (μ) and the electrophilicity (ω) [19,20] were studied. These parameters give information on the chemical reactivity of the studied molecules in their gas and solution media. The trends of the quantum chemical parameters are almost similar in both gas and solution media. A higher E_{HOMO} suggests a lower capability of accepting electrons because this energy describes the electron donating ability of a molecule. The E_{LUMO} indicates the ability of a molecule to accept electrons. Thus, the lower the value of E_{LUMO} , the more probable the molecule would accept electrons. Based on quantum molecular descriptors

Local Molecular Reactivity

The Fukui indices permit the distinction between the reactive regions of a molecule, the nucleophilic and

electrophilic behaviors of a molecule and the chemical reactivity [17]. Q_{N+1} corresponds to an anion in which an electron is added. Now consider the equations

$$f^+ = Q_{N+1} - Q_N$$

$$f^- = Q_N - Q_{N-1}$$

. Q_{N-1} corresponds to a cation in which an electron is removed from the HOMO. Thus Q_{N+1} , Q_N and Q_{N-1} are anionic, neutral and cationic states of a material, respectively. The maximum of f^+ corresponds to a reaction with respect to nucleophilic attack and the maximum of f^- shows the preferred site for adsorption of electrophilic agents. For dosulepin, the highest f^+ is associated with S atom and the highest f^- occurs at N atom in both gas and solution media.

CONCLUSIONS

Theoretical studies of the vibrational spectra, molecular structure and thermodynamic properties of doxepin were studied in gas and solution media by GGA-BLYP and GGA-PW91 modeling methods. Computational and chemical simulations were carried out for these drugs. Values have been assigned to the vibrational frequencies of the fundamental modes of these compounds. The BLYP/PW91 analyses of the wavenumbers show that the frequencies assigned to doxepin are higher. The bond length of C-O is shorter than that of C-S. The shorter bond length of C-O is responsible for the appearance of the high frequency peaks in compounds infrared spectra. The Fukui index results show that the site for electrophilic attack is an N atom in doxepin molecules. Doxepin can be attractive drugs for further medicinal and pharmacological studies.

REFERENCES

- [1] Stolerman, I. P.: *Encyclopedia of psycho-pharmacology*; Springer Science & Business Media, 2010, Vol. 2.
- [2] Jalander, L.; Oksanen, L.; ähtinen, J. Synthesis of dothiepin and doxepin by grignard reactions in toluene. *Synthetic Commun.*, **1989**, *19*, 3349-3352, DOI: 10.1080/00397918908052739.
- [3] Sankaranarayanan, R.; Siva, S.; Venkatesh, G.; Prabhu, A. A. M.; Rajendiran, N. Dual fluorescence of dothiepin, doxepin drugs-effect of solvents and β - cyclodextrin. *J. Mol. Liq.*, **2011**, *161*, 107-114, DOI: 10.1016/j.molliq.2011.04.016.
- [4] More details about DMol³ can be found at <http://www.accelrys.com/mstudio/DMol3.html>.
- [5] Delley, B. An all-electron numerical method for solving the local density functional for polyatomic molecules. *J. Chem. phys.*, **1990**, *92*, 508-517, DOI:10.1063/1.458452.
- [6] Delley, B. Fast calculation of electrostatics in crystals and large molecules. *J. Phys. Chem.*, **1996**, *100*, 6107-6110, DOI: 10.1021/jp952713n.
- [7] Becke, A. D., A multicenter numerical integration scheme for polyatomic molecules. *J. Chem. phys.*, **1988**, *88*, 2547-2553, DOI: 10.1063/1.454033.
- [8] Perdew, J. P.; Wang, Y. Accurate and simple analytic representation of the electron-gas correlation energy. *Phys. Rev. B*, **1992**, *45*, 13244, DOI: 10.1103/PhysRevB.45.13244.
- [9] Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a

- functional of the electron density. *Phys. Rev. B*, **1988**, 37, 785-789: 10.1103/PhysRevB.37.785.
- [10] Andzelm, J.; Kölmel, C.; Klamt, A. Incorporation of solvent effects into density functional calculations of molecular energies and geometries. *J. Chem. Phys.*, **1995**, 103, 9312-9320, DOI: 10.1063/1.469990.
- [11] Shigeru, O., *Organic Sulfur Chemistry: Structure and Mechanism*. London: CRC Press, 1991.
- [12] Roeges, N. P., *A guide to the complete interpretation of infrared spectra of organic structures*; Wiley, 1994.
- [13] Varsányi, G., *Assignments for vibrational spectra of seven hundred benzene derivatives*; Halsted Press, 1974, Vol. 1.
- [14] George, S., *Infrared and Raman Characteristic Group Frequencies-Tables and Charts*. Wiley, Chichester, **2001**.
- [15] Silverstein, R. M.; Webster, F. X.; Kiemle, D.; Bryce, D. L., *Spectrometric identification of organic compounds*; John Wiley & Sons, 2014.
- [16] Kundoo, S.; Banerjee, A.; Saha, P.; Chattopadhyay, K. Synthesis of crystalline carbon nitride thin films by electrolysis of methanol-urea solution. *Mater. Lett.* **2003**, 57, 2193-2197, DOI: 10.1016/S0167-577X(02)01172-2.
- [17] Chattaraj, P. K.; Sarkar, U.; Roy, D. R., Electrophilicity index. *Chem. Rev.* **2006**, 106, 2065-2091, DOI: 10.1021/cr040109f.

