Charge Density and Solvation Studies of Benzoxazole and its Derivatives-2-phenyl benzoxazole and 4-Amino-2-phenyl benzoxazole

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In the present work, biologically important molecules benzoxazole and its derivatives 2-phenyl benzoxazole and 4-amino-2-phenyl benzoxazole were investigated theoretically using molecular orbital and density functional theory. Semi empirical MO calculations, AM1 procedure, have been carried out on these molecules. These include charge density, heat of formation, ionization potential, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies and energy gaps. Solvation analysis on these compounds have been carried out by the polarizable continuum model (PCM) at the B3LYP with 6-31G* level of theory. The effects of electrostatic and non-electrostatic interaction contribution to free energy of solvation were discussed.

Key Words: Charge density, Solvention, Benzoxazole, 2-Phenyl benzoxazole, 4-Amino-2-phenyl benzoxazole.

INTRODUCTION

In the recent past, the heterocyclic organic molecules have achieved considerable importance because many of these molecules form an integral part of biologically important compounds and have various uses such as photo conducting materials[1] and as herbicides in agriculture[2] have not received much attention. Benzoxazole and its derivatives were studied extensively for their antitumour, antiviral and antibiotic properties as the new nonnucleosides topoisomerase 1 poisons, HIV-1 reverse transcriptase inhibitors and potent DNA gyrase inhibitors[3-7]. Although the literature is wealthy in information related to the biological activities of benzoxazole and its derivatives it seems a lack of any correlations between chemical behaviour, electronic structure and its solvation effects.

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The main aim of the present work is to carry out molecular orbital (MO) calculations were performed using AM1 procedure on benzoxazole and its derivatives to investigate the heat of formation, atomic charge distribution, ionization potential and orbital energies. In order to estimate the free energy of solvation of these compounds in various solvents, namely, water, acetone, methanol, ethanol, chloroform, carbon tetra chloride and benzene, we used the B3LYP/6-31G* basis set function of the density functional theory (DFT), which are included in the GAMESS package program.

THEORETICAL CALCULATIONS

Molecular orbital calculations give valuable information about the structure of the molecules, which actually be used to support the experimental evidence. The semi-empirical MO calculations were used in the present study is the Austin Model 1 (AM1) procedure described by Dewar *et al.*[8]. Solvation analysis conducted in this research was performed using the B3LYP method included in the GAMESS package program[9] together with the 6-31G* basis set function of the density functional theory (DFT). The minimum potential energy of these molecules were obtained from AM1 semi empirical calculations were solvated with various different solvents using a polarizable continuum model (PCM) by STO-6-31G* basis set with B3LYP density functional theory level.

RESULTS AND DISCUSSION

Computational quantum chemistry calculations can help identify and provide ways to obtain important chemical and physical information that cannot be easily obtained by experimental approaches. Figs. 1-3 shows the numbering of benzoxazole, 2-phenyl benzoxazole and 4-amino 2-phenyl benzoxazole skeleton that helps in ordering of charge distribution. The AM1 semi empirical method was first used to conduct calculations until convergence was achieved. Using the optimization of the geometric calculations, thermodynamic properties such as orbital energy, ionization energy, energy gap between highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) and heat of formation, *etc.*, of each of these molecules were obtained. Table-1 lists the calculated values of first ionization potential, HOMO, LUMO and energy gap of the molecules under study. Table-1 also shows that benzoxazole has higher ionization potential and its values decreasing in the order as follow:

Benzoxazole > 2-phenyl benzoxazole > 4-amino 2-phenyl benzoxazole. So, the stability of benzoxazole is more than that of both 2-phenyl benzoxazole and 4-amino 2-phenyl benzoxazole. It was also confirmed by the heat of formation (HOF) and HOMO & LUMO values. The resulting thermodynamic properties are of special importance and value.
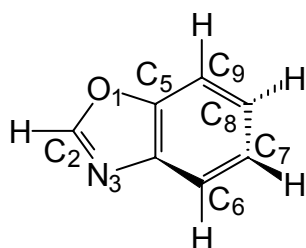
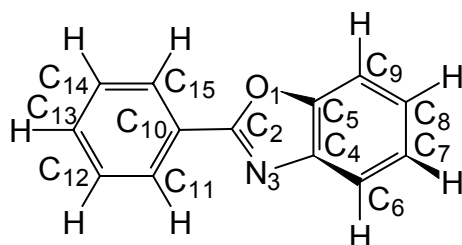Fig. 1. Structure and numbering of benzoxazole

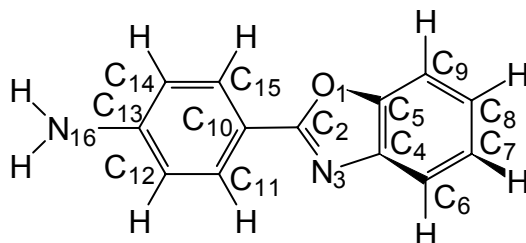Fig. 2. Structure and numbering of 2-phenyl benzoxazole

Fig. 3. Structure and numbering of 4-amino-2-phenyl benzoxazole

TABLE-1
COMPARISON OF HOMO, LUMO, ENERGY GAPS IONIZATION
POTENTIAL (eV), HEAT OF FORMATION (kcal/mol) AND DIPOLE
MOMENT (D) OF BENZOXAZOLE AND ITS DERIVATIVES

Parameters	Benzoxazole	2-phenyl benzoxazole	4-amino-2-phenyl benzoxazole
HOMO	-9.482	-8.965	-8.421
LUMO	-0.338	-0.734	-0.569
IP	9.482	8.965	8.421
HOF	31.347	59.887	55.819
Dipole moment	1.205	1.025	2.604
Energy gap	9.144	8.231	7.852

Atomic charge distribution: The charge distributions on different atoms for these three compounds were summarized in Table-2. There is no appreciable change in the electronic distribution at nitrogen and oxygen atom in benzoxazole, 2-phenyl benzoxazole and 4-amino 2-phenyl benzoxazole. The carbon atom (C2) in between oxygen and nitrogen is electronegative in benzoxazole (-0.0109), where as it is electropositive in 2-phenyl benzoxazole (0.0930) and 4-amino 2-phenyl benzoxazole (0.1091) is due to the electron withdrawing power of phenyl group in the moiety at C2. All the ring carbon atoms are electronegative, but carbon atom (C13) in 4-amino 2-phenyl benzoxazole is electropositive is mainly due to the electron rupture from electron pairs on nitrogen atom. The carbon C10 atom is connected with C2 atom charge distribution in 4-amino 2-phenyl benzoxazole (-0.0414) is slightly high electronegative compared to 2-phenyl benzoxazole (-0.0979). The dipole moments of benzoxazole, 2-phenyl benzoxazole and 4-amino 2-phenyl benzoxazole are 1.205, 1.025 and 2.604 D, respectively was calculated and reported in Table-1. The higher dipole moment value in 4-amino 2-phenyl benzoxazole is due to the NH_2 group. The higher dipole moment leads to very weak stability of 4-amino-2-phenyl benzoxazole was due to weak bonds.

TABLE-2
ATOMIC CHARGE DISTRIBUTIONS OF BENZOXAZOLE,
2-PHENYL BENZOXAZOLE AND 4-AMINO-2-PHENYL
BENZOXAZOLE

S. No.	Atom	Benzoxazole	2-phenyl benzoxazole	4-amino-2-phenyl benzoxazole
1	O_1	-0.1356	-0.1341	-0.1382
2	C_2	-0.0109	0.0931	0.1091
3	N_3	-0.1275	-0.1290	-0.1417
4	C_4	-0.0869	-0.0793	-0.0744
5	C_5	-0.0126	-0.0104	-0.0134
6	C_6	-0.0644	-0.0682	-0.0722
7	C_7	-0.1467	-0.1463	-0.1459
8	C_8	-0.1099	-0.1118	-0.1156
9	C_9	-0.1128	-0.1143	-0.1140
10	C_{10}	–	-0.0414	-0.0979
11	C_{11}	–	-0.0813	-0.0368
12	C_{12}	–	-0.1415	-0.2136
13	C_{13}	–	-0.1057	0.1003
14	C_{14}	–	-0.1402	-0.2115
15	C_{15}	–	-0.0888	-0.0442
16	N_{16}	–	–	-0.3416

Solvation analysis: Solvation effects play an important role in determining chemical structure and reactivity. The important role of the solvents on the outcome and kinetics of chemical reactions is well established[10-23]. Solvation effects are also very important for electronic spectroscopy[24]. In the present work, polarizable continuum model (PCM) has been employed in the computation of free energy of solvation for benzoxazole, 2-phenyl benzoxazole and 4-amino-2-phenyl benzoxazole in acetone, benzene, carbon tetra chloride, chloroform, methanol, ethanol, water and the results were discussed. The free energy of solvation ΔG_{sol} is the algebraic sum of electrostatic ΔG_{el} and non-electrostatic interaction ΔG_{nel} energy. The free energy of solvation represents a important property for the thermodynamical description of a solution with impact in the chemical, biological and pharmaceutical sciences.

Electrostatic interaction: Electrostatic interaction plays an important role in determining the structure and functions of biological molecules[25-27]. The computed electrostatic, non-electrostatic and total interaction energy and induced dipole moment of benzoxazole, 2-phenyl benzoxazole and 4-amino 2-phenyl benzoxazole in different solvents are evaluated by PCM method and the data are tabulated in the Tables 3-5. It is observed that electrostatic interaction energies of benzoxazole, 2-phenyl benzoxazole and 4-amino-2-phenyl benzoxazole is quite large negative values in protic solvents namely, water, methanol, ethanol and acetone and very less in aprotic solvents, carbon tetra chloride and benzene and medium in chloroform solvent. The magnitudes of negative electrostatic interaction energies are in the increasing order as follows: benzoxazole < 2-phenyl benzoxazole < 4-amino-2-phenyl benzoxazole due to its polarizability. The same reason accounts for a large induced dipole moment. The solute-solvent interaction is mainly dipole-dipole attraction. In order to express the solute-solvent interaction, the induced dipole moment values are calculated and presented in Tables 3-5. The induced dipole moments of water, acetone, methanol and ethanol are higher than those of other solvents. This value indicates a strong solute- solvent interaction mainly in the mixtures of the compounds under study in water, acetone, ethanol and methanol. This is also supported by higher electrostatic interaction in this medium.

Non-electrostatic interaction: The non-electrostatic interaction contribution is regarded as playing minor role, but it is important for a fine turning of the solvation process modeling. This contribution can be separated in to cavity formation free energy, dispersion and repulsion contribution. In the quantum mechanical approach to free energy of solvation by the polarizable continuum model, it has been observed that larger cavities cause more negative ΔG_{sol} simply due to increasing distance between solute and solvent. The dispersion energies are due to polarization of the

TABLE-3
FREE ENERGY OF SOLVATION AND ITS COMPONENTS AND
INDUCED DIPOLE MOMENT OF BENZOXAZOLE IN DIFFERENT
SOLVENTS

Solvent	ΔG_{el}	ΔG_{nel}	ΔG_{sol}	μ_{ind}
H_2O	-7.99	9.85	1.85	1.788
CH_3COCH_3	-7.48	5.14	-2.33	1.758
CH_3OH	-7.73	5.23	-2.49	1.773
$C_2H_5OH_5$	-7.58	5.58	-1.99	1.764
$CHCl_3$	-5.54	5.35	-0.19	1.644
CCl_4	-3.26	5.89	2.63	1.505
C_6H_6	-3.29	7.02	3.73	1.507

TABLE-4
FREE ENERGY OF SOLVATION AND ITS COMPONENTS AND
INDUCED DIPOLE MOMENT OF 2-PHENYL BENZOXAZOLE IN
DIFFERENT SOLVENTS

Solvent	ΔG_{el}	ΔG_{nel}	ΔG_{sol}	μ_{ind}
H_2O	-9.17	16.26	7.08	1.514
CH_3COCH_3	-8.48	8.8	0.32	1.492
CH_3OH	-8.82	8.84	0.02	1.491
$C_2H_5OH_5$	-8.63	9.49	0.86	1.497
$CHCl_3$	-6.12	9.05	2.94	1.355
CCl_4	-3.48	9.96	6.47	1.228
C_6H_6	-3.52	11.78	8.26	1.231

TABLE-5
FREE ENERGY OF SOLVATION AND ITS COMPONENTS AND
INDUCED DIPOLE MOMENT OF 4-AMINO-2-PHENYL
BENZOXAZOLE IN DIFFERENT SOLVENTS

Solvent	ΔG_{el}	ΔG_{nel}	ΔG_{sol}	μ_{ind}
H_2O	-13.42	17.49	4.07	3.765
CH_3COCH_3	-12.35	9.51	-2.85	3.706
CH_3OH	-12.87	9.53	-3.33	3.727
$C_2H_5OH_5$	-12.56	10.24	-2.32	3.718
$CHCl_3$	-8.95	9.79	0.84	3.542
CCl_4	-5.14	10.76	5.63	3.357
C_6H_6	-5.19	12.73	7.54	3.361

Energies are in kcal/mol & induced dipole moment (μ_{ind}) are in Debye.

solvent molecules by the solute molecules. This polarization, in turn, may depend on the dipole moment of the solvent molecule. The dielectric constants as well as the molecular size of the solvent molecules determine the repulsive energies. It is observed that non-electrostatic contribution of the solute in water solvent is large compared to other solvents. It is due to the fact that large dielectric constant and induced dipole moment values of water. But, non-electrostatic contribution of the solute in acetone solvent is less compared to other solvents. It may be noted that the free energy of solvation is negative is due to the less non-electrostatic interaction between the solute and solvent. The total interaction energy is positive in phenyl benzoxazole in all the different solvents, because non-electrostatic contribution dominates more than that of electrostatic contribution.

Conclusion

The quantum mechanical solvation analyses have been carried out for benzoxaole, 2-phenyl benzoxazole and 4-amino-2-phenyl benzoxazole. The computed physical properties such as free energy of solvation and its contribution, dipole moments and induced dipole moments were discussed. Semi empirical MO calculations were utilized to compute some important thermodynamic properties such as orbital energy, HOMO, LUMO, ionization potentials and energy gap for the benzoxazole, 2-phenyl benzoxazole, 4-amino-2-phenyl benzoxazole were discussed. The interaction between the benzoxazole and its derivatives and various solvents were investigated to explain the condensed phase simulation, which will be useful for the study of solvation of the benzoxazole, 2-phenyl benzoxazole, 4-amino-2-phenyl benzoxazole. The computed thermodynamic properties are useful to determine the stability and chemical reactivity of these compounds.

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