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RESEARCH ARTICLE

INVESTIGATION OF STRUCTURAL AND REACTIVITY PROPERTIES OF SOME HALOGENATED PIPERAZINES

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ABSTRACT

The chemical and biological activities are strongly related to the molecular structures and the media to which the molecules were subjected. Therefore, it is crucial to know the behaviors of molecular systems in the examined solvent media and their structural and reactivity properties. In the framework of this study, molecular and reactivity properties of some halogenated piperazine derivatives were undertaken by using the density functional theory. It was observed that halogen atoms have considerable effects on the behavior of piperazine molecule. Further, the atypical characteristic of fluorine affecting conformational preference is observed for di-halogenated piperazines with the same halogen atoms.

Keywords: DFT, Halogen effect, Molecular structure, Reactivity properties

1. INTRODUCTION

Piperazine derivatives are considered special types of compounds which were found in large scale applications possibilities in various fields of science. For example, piperazine and its derivatives have been found as a component in different marketed drugs [1]. Piperazines were also used as a starting material to synthesize many different compounds [2, 3]. Recently, Lipin et. al reported the effect of piperazine substituted Favipiravir drug molecule against the Nipah virus [4]. Further, many piperazine derivatives have been also known for their antihelmintic effect [5].

Density functional theory (DFT) has been extensively used to probe the molecular structures, spectroscopic and reactivity properties of many different compounds ranging from small to macromolecules depending on the computational source available [6-8]. In the essence of DFT, by taking the electron density as a major parameter, it is possible to understand the ground and also excited states of molecular structures and many other electronic properties of the investigated systems [9].

Stable molecular structures are closely related to chemical or biological activities. Therefore, in continuation with our interests in the investigation of piperazine derivatives [10-12], the prime objective of this search is to predict the stable molecular structures of the examined halogenated piperazines. Within this objective, we have examined the conformational and reactivity properties of the compounds together with the halogen and solvent effects. The compounds studied, their names and the abbreviations used are summarized as follows; $C_4H_{10}N_2$: piperazine (p), $C_4H_9FN_2$: 1-fluoropiperazine (1-fp), $C_4H_9ClN_2$: 1-chloropiperazine (1-cp), $C_4H_9BrN_2$: 1-bromopiperazine (1-bp), $C_4H_9ClFN_2$:1-chloro-4-fluoropiperazine (1-cfp), $C_4H_9BrFN_2$:1-fluoro-4-bromopiperazine (1-fbp), $C_4H_9BrClN_2$:1-bromo-4-chloropiperazine (1-bcp), $C_4H_8F_2N_2$: 1,4-difluoropiperazine (1,4-fp), $C_4H_8Cl_2N_2$: 1,4-dichloropiperazine (1,4-cp), $C_4H_8Br_2N_2$: 1,4-dibromopiperazine (1,4-bp).

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2. CALCULATIONS

As seen in Figure 1, the calculations were focused on every four conformers (ee, ae, ea, aa, e: equatorial and a: axial) of the ten compounds. These conformational notations are also in line with the order of the abbreviations of the molecules. The first character of the ae and ea symbols represents the position of halogen atoms for 1-fp, 1-cp and 1-bp. Similarly, for 1-fbp, 1-cfp and 1-bcp, the first character of ae and ea shows fluorine, chlorine and bromine halogen atoms correspondingly.

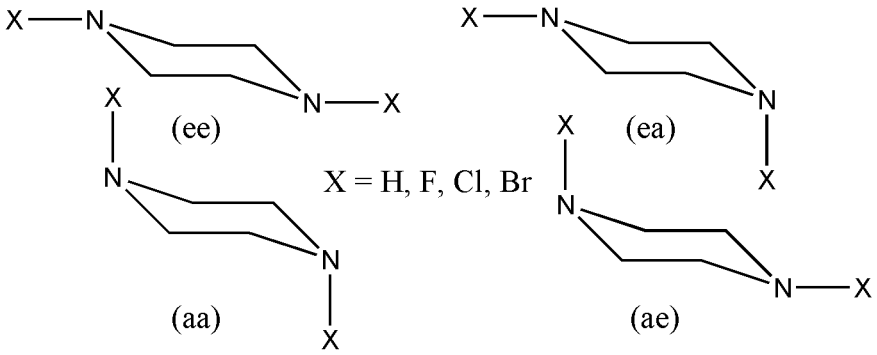

Figure 1. Conformational isomer and notation for the compounds.

Calculations were carried out in the gas phase, benzene and water media using the B3LYP functional with the cc-pvdz basis set. The polarizable continuum model in which the solvent is considered as a continuous medium was used to understand the solvation effect [13]. Computations were performed using the Gaussian 16 program package [14]. GaussView was used for building molecules and visualization of molecular orbitals [15].

3. RESULTS AND DISCUSSIONS

3.1. Conformational Studies

Piperazine in the chair form is more stable than the skewed boat by ~8 kcal/mol and the most stable conformation is ee chair conformer. This form is predominant in pure solids whereas the strongly dipolar ea form is most stabilized in an aqueous solution [16]. Relative stabilities and mole fractions for the optimized structures of the conformers of the compounds in different environments are given in Table 1. Regarding the calculations by B3LYP/cc-pvdz in the gas phase, benzene and water, the ee form is more stable than ea (ae) and aa 0.36 / 1.16, 0.29 / 0.93 and 0.18 / 0.60 kcal/mol, respectively. For the gas phase, piperazine prefers ee, ea (ae) and aa conformers with probabilities of 59.28%, 32.38% and 8.34% correspondingly. These results are also suitable with MP2 and B3LYP calculations with the aug-cc-pvdz basis set [16]. Similarly, for benzene and water, the molecule prefers the ee form with approximate probabilities of 55% and 48% respectively and the percentage of the most stable form has decreased. It is observed that the most stable form of piperazine is independent of the medium and methods.

Table 1. Relative energy (kcal/mol) and mole fraction (%) for conformers of the compounds.

Molecule	Relative Energy	Mole Fraction	Relative Energy	Mole Fraction	Relative Energy	Mole Fraction
p	Gas		Benzene		Water	
aa	1.16	8.34	0.93	11.46	0.60	17.23
ea (ae)	0.36	32.38	0.29	33.75	0.18	35.15
ee	-	59.28	-	54.79	-	47.62
1-fp						
aa	1.55	3.43	1.50	4.13	1.33	6.42
ae	0.78	12.60	0.96	10.36	1.27	7.04
ea	-	47.25	-	52.33	-	60.66
ee	0.15	36.72	0.27	33.18	0.50	25.88
1-cp						
aa	2.58	0.63	2.51	0.78	2.32	1.26
ae	1.79	2.36	1.93	2.06	2.20	1.53
ea	-	48.81	-	53.96	-	63.54
ee	0.01	48.20	0.13	43.20	0.38	33.67
1-bp						
aa	2.45	0.81	2.39	0.99	2.22	1.55
ae	1.73	2.75	1.87	2.39	2.15	1.75
ea	-	51.05	-	56.47	-	65.97
ee	0.07	45.39	0.20	40.15	0.45	30.73
1-cfp						
aa	0.98	10.63	1.04	10.16	1.08	10.04
ae	-	55.60	-	58.62	-	62.11
ea	1.20	7.30	1.18	7.97	1.16	8.75
ee	0.44	26.47	0.55	23.25	0.70	19.09
1-fbp						
aa	0.95	11.17	1.02	10.40	1.07	10.10
ae	-	55.37	-	58.46	-	61.88
ea	1.22	7.04	1.21	7.54	1.20	8.20
ee	0.44	26.42	0.54	23.60	0.67	19.82
1-bcp						
aa	2.02	2.37	1.97	2.44	1.86	2.72
ae	1.04	12.39	0.93	14.05	0.80	16.32
ea	0.97	13.94	0.87	15.65	0.74	18.07
ee	-	71.30	-	67.86	-	62.89
1,4-fp						
aa	-	54.67	-	51.64	-	48.44
ae (ea)	0.25	35.78	0.15	39.83	0.05	44.60
ee	1.03	9.55	1.07	8.53	1.15	6.96
1,4-cp						
aa	2.05	2.56	1.99	2.77	1.85	3.30
ae (ea)	0.99	15.30	0.88	17.82	0.75	21.38
ee	-	82.14	-	79.41	-	75.32
1,4-bp						
aa	1.99	2.88	1.96	2.96	1.87	3.30
ae (ea)	1.03	14.48	0.94	16.42	0.82	19.31
ee	-	82.64	-	80.62	-	77.39

Turning to single halogenated piperazines as 1-fp, 1-cp and 1-bp, the most stable conformation is ea with a probability of 47-66% in the considered environments. Further, the percentage of the most stable form of the compounds has increased as one goes to the polar water environment (Table 1). The most stable form of the compounds is independent of the solvent and halogen atom.

According to the calculated energies of di-halogenated piperazines with different halogen atoms, 1-cfp and 1-fbp prefer ae form with approximate probabilities of 55-61% for the used media whereas the most stable form of 1-bcp is ee by the probabilities of 63-71%. As going to the polar water environment, the percentage of preference for the most stable form of 1-cfp and 1-fbp increases whereas it decreases for 1-bcp. The most stable conformer of these compounds is dependent on the halogen atom.

Moving to the optimization energy values of di-halogenated piperazines with the same halogens in the gas phase, benzene and water, the ee form of 1,4-cp and 1,4-bp is also more stable than other conformers with the approximate preference of 75-83% probabilities. When all compounds are considered, the data are the highest percentages. 1,4-fp, however, prefers aa form with the probabilities of 48-55%. The percentage of preference for the most stable form of the compounds decreases as going to the polar water environment. The most stable conformer of these di-halogenated piperazines is also dependent on the halogen atom.

3.2. Reactivity Properties

The frontier orbitals of a molecular system can be used to determine which part of the molecule can accept and donate electrons [17]. Therefore, distributions of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) as the ionization potential and electron affinity correspondingly are the indicators of molecular activity. A more negative LUMO value is reported as the descriptor of the potent biological activities of a given molecule [18]. The energy gap between these frontier orbitals is known as the electrical band gap (E_g) or transport gap. As an example, the reactivity parameters such as band gap, chemical hardness (η), Fermi energy (E_F) and electrophilicity index (ω) of the compounds in water are presented in Table 2.

Table 2. Reactivity parameters (eV) of the compounds in water.

Molecule	E_{HOMO}	E_{LUMO}	E_g	η	μ (E_F)	ω
p (ee)	-6.068	1.538	7.606	3.803	-2.265	0.674
1-fp (ea)	-6.393	0.566	6.959	3.480	-2.914	1.220
1-cp (ea)	-6.325	-1.118	5.207	2.604	-3.722	2.660
1-bp (ea)	-6.272	-1.693	4.579	2.290	-3.983	3.464
1-cfp (ae)	-6.745	-1.172	5.573	2.787	-3.959	2.812
1-fbp (ae)	-6.630	-1.755	4.875	2.438	-4.193	3.606
1-bcp (ee)	-6.733	-1.741	4.992	2.496	-4.237	3.596
1,4-fp (aa)	-6.389	0.470	6.859	3.430	-2.960	1.277
1,4-cp (ee)	-6.811	-1.190	5.621	2.811	-4.001	2.847
1,4-bp (ee)	-6.694	-1.748	4.946	2.473	-4.221	3.602

The band gap of piperazine in the gas phase, benzene and water is the highest value by 7.385, 7.479 and 7.606 eV correspondingly and it implies high kinetic stability and low chemical reactivity. However, the lowest value of the band gap belongs to 1-bp with 4.768, 4.688 and 4.579 eV respectively, and it is the most conductive. Further, these energy gaps of the compounds are sufficiently large to meet the viability criterion [19]. Similarly, 1-bp has the lowest value of chemical hardness for all media. 1,4-bp, 1-fbp and 1-bcp have more negative LUMO values than others in the gas phase, benzene and water, respectively. Similarly, these compounds have the highest value of the electrophilicity index. The density plots for HOMO and LUMO of 1-fbp in water are shown in Figure 2 as an example. HOMO is delocalized on almost all atoms except some H atoms, but LUMO is delocalized on almost all atoms except some H and halogen (F) atoms.

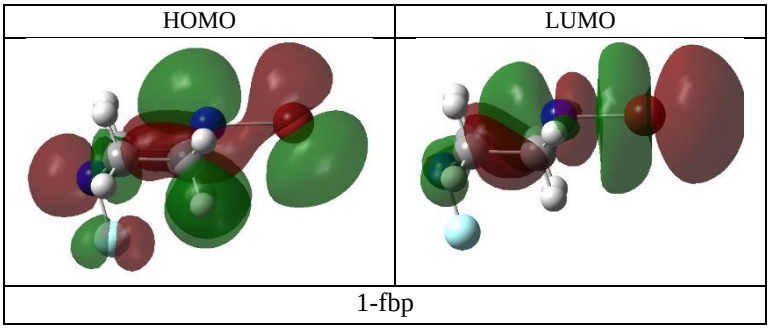

Figure 2. Frontier molecular orbitals of 1-fbp.

3. CONCLUSIONS

In the scope of this study, very detailed theoretical conformational analysis and reactivity parameters on halogenated piperazines were carried out. The main conclusions of this work are as follows: Conformational preference of all compounds is independent of the solvent but there is a halogen effect for di-halogenated piperazines with both different and same halogen atoms. Further, by comparing the energetic data of 1,4-fp with those of 1,4-cp and 1,4-bp, it is confirmed that fluorine has an atypical characteristic affecting conformational preference. The lowest value of band gap and chemical hardness belongs to 1-bp and it is the most conductive compound. The lowest band gap and chemical hardness values are independent of the solvent but there are both halogen and solvent effects on more negative LUMO and the highest electrophilicity index values. It can be said that 1,4-bp, 1-fbp and 1-bcp are more biologically active than others in the gas, benzene and water media.

CONFLICT OF INTEREST

The authors stated that there are no conflicts of interest regarding the publication of this article.

AUTHORSHIP CONTRIBUTIONS

All authors contributed equally.

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