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Araştırma Makalesi/Research Article

Conformational Analysis of N,N'-Phenylene-Diylbis[3-(1-Aminoethyl-6-Methyl-2H-Pyran-2,4(3H)-Dione]

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Abstract- **Conformational analysis of N,N'-phenylenediylbis[3-(1-aminoethyl)-6-methyl-2H-pyran-2,4(3H)-dione] was performed by using theoretical calculations. The possible stable conformers in keto-amine or imine-enol forms of N,N'-phenylenediylbis[3-(1-aminoethyl)-6-methyl-2H-pyran-2,4(3H)-dione] on their potential energy surfaces (PES) were investigated by using semi-empirical methods and hybrid-density functional theory (*h*-DFT) with the basis sets of different type and size. In the light of results from relative energies and population analysis, the more stable forms of N,N'-phenylenediylbis[3-(1-aminoethyl)-6-methyl-2H-pyran-2,4(3H)-dione were determined.**

***Keywords*- Conformational analysis, DFT, PES, N,N'-phenylenediylbis[3-(1-aminoethyl)-6-methyl-2H-pyran-2,4(3H)-dione], Tautomerism.**

I.INTRODUCTION

3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one and its dehydroacetic acid derivatives play essential role as starting products for the preparation of miscellaneous heterocyclic compounds due to the potential applications in medical industry, organic and inorganic synthesis [1,2]. Schiff bases heterocyclic systems derived from dehydroacetic acid are also well-known samples for the investigation of keto-enol tautomerism [3]. The effect of molecular conformation, substituents, solvents on the emergence of both enol-imine or keto-amine tautomer are widely studied diverse processes in solid state or solution phase. However, the available literature for Schiff bases comprised of either an enol-imino and keto-amino tautomeric moieties is still rather limited [3-7]. The molecular structure of such bases are generally characterized by the intensity of $NH \cdots O$ or $N \cdots HO$ intramolecular hydrogen bonds [5-7].

To the best of our knowledge, neither quantum chemical calculations nor the conformational analysis of N,N'-phenylenediylbis[3-(1-aminoethyl)-6-methyl-2H-pyran-2,4(3H)-dione] compound, have been reported in the open scientific literature to date. In this paper, we investigated the conformational analysis of N,N'-phenylenediylbis[3-(1-aminoethyl)-6-methyl-2H-pyran-2,4(3H)-dione]. The keto-enol tautomerism of title compound was also considered in conformational analysis. The feasible stable conformers of title molecule on its optimized potential energy surfaces (*o*-PES) were investigated by using Austin Model 1 (AM1), Parametric Method 5 (PM5) and Modified Neglect of Differential Overlap with D Atomic Orbitals (MNDO-d) semi-empirical Hamiltonians. The appropriate structures were defined with hybrid-density functional theory (h-DFT) and the full version of the Heyd-Scuseria-Ernzerhof functional (HSEH1PBE) method together with the basis sets of different type and size. Using the results from total electronic energy, self-consisted field energy, Gibbs energy as well as population analysis, more stable forms of N,N'-phenylene-diylbis[3-(1-aminoethyl)-6-methyl-2H-pyran-2,4(3H)-dione] molecule were determined in keto-amine and imine-enol forms.

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II.CONFORMATIONAL, ENERGY AND POPULATION ANALYZES

Calculations of o-PESs of N,N'-phenylenediylbis[3-(1- aminoethyl)-6-methyl-2H-pyran-2,4(3H)-dione] molecule were carried out with AM1, PM5 or MNDO-d methods by using the MOPAC2002 geometry optimization within CAChe Pro software [8]. To obtain the probable stable molecular structures of N,N'-phenylenediylbis[3-(1-aminoethyl)-6-methyl-2H-pyran-2,4(3H)-dione], the torsion angles τ_1(CCNC), τ_2(CCN'C'), τ_3(CNCC) and τ_4(CC'N'C') were iteratively changed by 3^0 (Figure 1 and Figure 2). The structures of possible conformers were pinned down by taking into account the maximum negative heat of formation energy (ΔH) (Figure 3) .

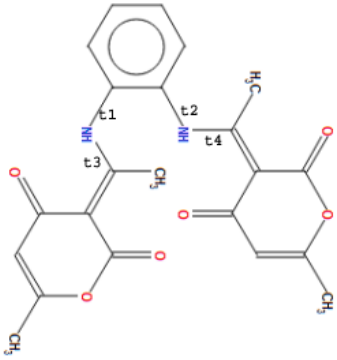

Figure 1. Keto-amine structure of N,N'-phenylenediylbis[3-(1- aminoethyl)-6-methyl-2H-pyran-2,4(3H)-dione]

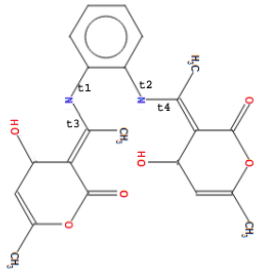

Figure 2. Imine-enol structure of N,N'-phenylenediylbis[3-(1- aminoethyl)-6-methyl-2H-pyran-2,4(3H)-dione]

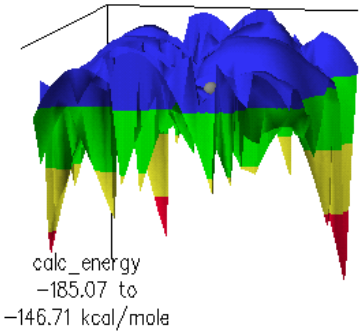

Figure 3. Optimized potential energy surfaces of keto-amine form of title compound in PM5 method

Full geometry optimization was performed for the selected conformers via Becke-3-Lee–Yang–Parr (B3LYP) hybrid-Density Functional Theory (h-DFT) method with 6-31G(d,p) basis set within the Gaussian03W program package [9]. Vibrational frequency analysis was also carried out using the same functional and basis set to confirm the nature of the ground state structures on the *o*-PES.

In many cases, additional diffuse and polarization functionals added to the basis set were used in the electronic structure calculations of Schiff based heterocyclic systems. They give rise to more accurate results due

to the highly delocalized electrons [10]. In addition, it is very important which method of h-DFT is used in theoretical calculations. The widely used first generation method is B3LYP. The B3LYP includes Becke's three-parameter hybrid functional (B36) which combines various proportions of local and nonlocal treatments for exchange-correlation with Hartree–Fock (HF) exchange with gradient-corrected electron correlation of Lee-Yang-Parr (LYP) functional. Another popular second-generation method is the recommended version of the full Heyd-Scuseria-Ernzerhof hybrid exchange-correlation functional (HSE06) with Perdew, Burke, and Ernzerhof's exchange and correlation functions (PBE). The abbreviation of second-generation method is HSEH1PBE. HSEH1PBE method uses a short-range exact hybrid exchange functional and a long-range semilocal hybrid density functional in combination with PBE potential. The reason is that such functionals are intended to regain some of the necessary features of the hybrid compounds in solid-state or solution phase calculations. In the last two decade, several studies researching the performance of h-DFT functionals reported that HSEH1PBE method achieves more accurate results for organic compounds [11].

For testing the stability of conformers and providing more accurate results for conformation, energy and population analyzes, we were decided to use both B3LYP and HSEH1PBE levels of theory. For this reason, the geometry optimization and vibrational frequency computations were performed at B3LYP/6-31+G(d,p), B3LYP/6-311++G(d,p) and HSEH1PBE/6-311++G(d,p) levels of theory. From conformational calculations, twenty conformers were degraded to ten conformers by using reflection symmetry operation through a mirror plane. The molecular structure illustrations for five keto-amine (KA) conformers of title compound are depicted in Figure 4. The other five imine-enol (IE) conformers are also given in Figure 5.

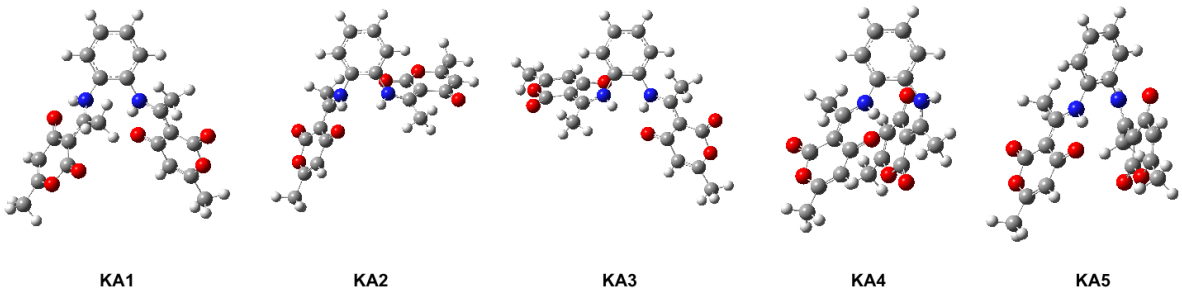

Figure 4. The molecular structure illustrations for five stable keto-amine conformers of title compound

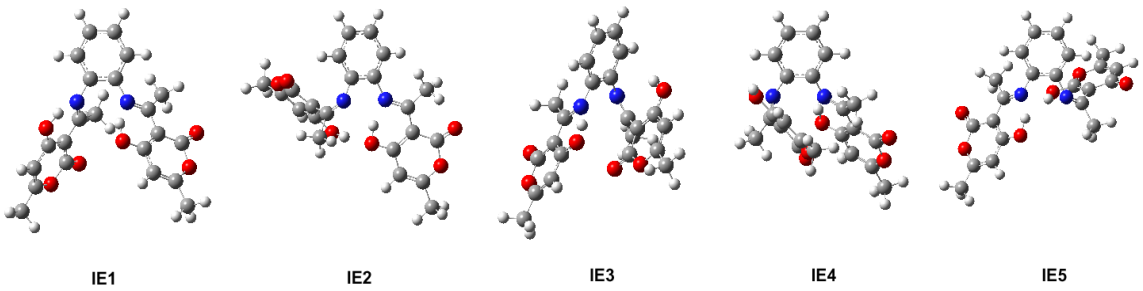

Figure 5. The molecular structure illustrations for five stable imine-enol conformers of title compound

Population analysis of ten conformers was implemented by using statistical thermodynamic factors which include conformational relative energies having major contributions from harmonic vibrational modes [12]. The statistical Boltzmann factors of the population analysis were set up on the basis of Gibbs free energy (ΔG). The Boltzmann weighting factors (N_i) were computed for each conformer by using the following relation,

$$N_i = exp(-\Delta G_i/RT)/\sum \exp(-\Delta G_i/RT) \quad (1)$$

where R=1.987x10^{-3} kcal/mol, ΔG_i is Gibbs free energy of conformer *i* and T=298.15 K was used.

Possible stable keto-amine and imine-enol conformers for the N,N'-phenylenediylbis[3-(1- aminoethyl)-6-methyl-2H-pyran-2,4(3H)-dione] compound and their some molecular features are given in Table 1 and Table 2. The tables point out that the KA-1 conformer in keto-amine forms and the IE-1 conformer in imine-enol forms are the more stable forms of title compound at room-temperature among the other conformers considering the

relative energies together with the population analysis values. It is also worth noticing that the effect at various basis sizes on relative energies is negligible, the stability for the conformers remains the same order and whole conformers are assimilated C1 symmetry group having no symmetry element.

The stability order of conformers may be due to the $NH \cdots O$ or $N \cdots HO$ intramolecular hydrogen bonds. The intensity of intramolecular hydrogen bond determines the stability of tautomeric forms for the compound. The IE-1 form is more stable than KA-1 form which is having strong $N \cdots OH$ intramolecular hydrogen bonds at B3LYP/6-31g(d,p) level of theory. However, the KA-1 form is more stable than IE-1 form owing to having strong $NH \cdots O$ intramolecular hydrogen bonds at B3LYP/6-311++g(d,p) level of theory. On the other hand, the results of energy calculations for KA-1 and IE-1 forms at HSEH1PBE theory level have exactly same values. In the light of these results, the HSEH1PBE theory level may be more accurate to predict the intensity of $NH \cdots O$ and $N \cdots HO$ intramolecular hydrogen bonds of title compound in gas phase.

Table 1. The some molecular features for the possible stable keto-amine (KA) and imine-enol (IE) conformers of title compound at B3LYP/6-31g(d,p) and B3LYP/6-31+g(d,p) theory levels

Conformer	B3LYP/6-31g(d,p)					B3LYP/6-31+g(d,p)				
	μ_{TOTAL} (Debye)	ΔE(Total) (kcal/mol)	ΔE(SCF) (kcal/mol)	δΔG (kcal/mol)	Ni (%)	μ_{TOTAL} (Debye)	ΔE(Total) (kcal/mol)	ΔE(SCF) (kcal/mol)	δΔG (kcal/mol)	Ni (%)
KA-1	2.82	0.00	0.00	0.00	100.00	2.93	0.00	0.00	0.00	100.00
KA-2	2.10	11.73	11.65	11.14	00.00	2.45	11.33	11.22	10.76	00.00
KA-3	1.48	12.10	12.12	11.71	00.00	1.37	12.11	11.84	11.72	00.00
KA-4	3.39	13.44	13.23	14.24	00.00	3.38	13.62	13.36	13.90	00.00
KA-5	2.98	24.47	15.19	15.20	00.00	3.05	14.77	14.83	13.29	00.00
IE-1	3.70	0.00	0.00	0.00	100.00	3.88	0.00	0.00	0.00	100.00
IE-2	4.14	7.28	5.46	7.82	00.00	4.27	6.90	5.06	7.05	00.00
IE-3	5.53	14.98	14.70	15.36	00.00	5.80	14.46	14.22	14.55	00.00
IE-4	5.73	19.15	18.84	19.58	00.00	6.16	18.22	17.92	18.00	00.00
IE-5	2.48	23.32	22.44	23.64	00.00	2.69	22.55	21.79	22.42	00.00

The total electronic energy (Total)), self-consistent field (SCF), and Gibbs free energy (ΔG) of the conformers were defined with regard to calculated value of the *keto-amine-1* (KA-1) or *imine-enol-1* (IE-1) conformers. N_i, is the percentage value of Boltzmann weighting factors obtained as a result of population analysis.

Table 2. The some molecular features for the possible stable keto-amine (KA) and imine-enol (IE) conformers of title compound at B3LYP/6-311++g(d,p) and HSEH1PBE /6-311++g(d,p) theory levels

Conformer	B3LYP/6-311++g(d,p)					HSEH1PBE/6-311++g(d,p)				
	μ_{TOTAL} (Debye)	ΔE(Total) (kcal/mol)	ΔE(SCF) (kcal/mol)	δΔG (kcal/mol)	Ni (%)	μ_{TOTAL} (Debye)	ΔE(Total) (kcal/mol)	ΔE(SCF) (kcal/mol)	δΔG (kcal/mol)	Ni (%)
KA-1	3.00	0.00	0.00	0.00	100.00	2.59	0.00	0.00	0.00	100.00
KA-2	2.51	10.72	10.66	10.21	00.00	2.27	12.41	11.96	12.09	00.00
KA-3	1.46	11.60	11.40	11.29	00.00	1.03	12.91	12.28	12.43	00.00
KA-4	3.43	12.95	12.76	13.03	00.00	3.22	13.50	12.90	14.00	00.00
KA-5	3.14	14.08	14.17	13.70	00.00	2.80	15.20	14.78	15.47	00.00
IE-1	3.84	0.00	0.00	0.00	100.00	2.59	0.00	0.00	0.00	100.00
IE-2	4.09	5.79	4.27	6.03	00.00	4.00	12.16	8.70	12.50	00.00
IE-3	5.65	13.51	13.4	13.66	00.00	5.65	16.06	16.37	16.08	00.00
IE-4	6.16	17.11	17.03	16.92	00.00	7.31	19.99	20.26	19.82	00.00
IE-5	2.66	21.78	21.23	21.67	00.00	3.42	25.27	25.03	25.18	00.00

The total electronic energy (Total)), self-consistent field (SCF), and Gibbs free energy (ΔG) of the conformers were defined with regard to calculated value of the *keto-amine-1* (KA-1) or *imine-enol-1* (IE-1) conformers. N_i, is the percentage value of Boltzmann weighting factors obtained as a result of population analysis.

III. CONCLUSION

The conformational behaviour of N,N'-phenylenediylbis[3-(1-aminoethyl)-6-methyl-2H-pyran-2,4(3H)-dione] compound was investigated in this study for the first time. Results of relative energy calculations for gas phase indicate that KA-1 tautomeric form is the most stable conformer in keto-amine forms of N,N'-phenylenediylbis[3-(1-aminoethyl)-6-methyl-2H-pyran-2,4(3H)-dione] compound. In terms of imine-enol form of title compound, IE-1 tautomeric form is the most stable conformer. Furthermore, the relative energies of other conformers at B3LYP and HSEH1PBE theory levels are larger than 4.0 kcal/mol. Therefore, Boltzmann weighting factors for population analysis of the other eight conformers could be neglected and these results suggest that conformational energy barrier is independent of the methods or basis sets.

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