Computational approach on chemical reactivity of Beta-Mercaptoethylamine

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Abstract

Beta-Mercaptoethylamine is a radiation-protective agent that oxidizes in air to form Cysteamine given intravenously or orally to treat radiation sickness. The compound has been investigated by spectroscopy quantum chemistry methods namely DFT using Gaussian 09 software package. Frontier molecular orbital analysis that explains the energy gap between the ground state HOMO and the first excited state LUMO energies were determined. Besides molecular global reactivity descriptors, MESP, electron localization function (ELF) and localized orbital locator (LOL) analysis, Condensed Fukui function, Bond dissociation energy for hydrogen abstraction (H-BDE) were calculated for the title compound. The formation of donor and acceptor stabilization energies, molecular bonding composed from orbitals localized on different atoms and molecular bond angular properties were investigated using NBO, NLMO and NHO calculations.

Keywords: DFT; MESP; NBO; NLMO; Condensed Fukui function;

1. Introduction

Beta-Mercaptoethylamine is a chemical compound used in the treatment of cystinosis. It is a simple aminothiols molecule used to treat nephropathic cystinosis, a lysosomal storage disease characterised by the abnormal accumulation of the amino acid and cystine [1]. It is a stable aminothiols, an organic compound containing both an amine and a thiol functional groups. It is a conjugate base of a cysteaminium [2]. It is a white, water soluble solid often used as salts of ammonium derivative [$\text{HSCH}_2\text{CH}_2\text{NH}_3$] [3] including the hydrochloride, phosphocysteamine and bitartrate [4]. The most important adverse effect related to topical use is skin irritation.

2. Computational details

All theoretical calculations were carried out with Gaussian 09 program package [5] using B3LYP [6-7] methods in conjunction with 6-311 +G(d,p) basis set. The molecular structure, MEP surfaces were visualized with Gauss View 5 program [8].

3. Results and Discussions

3.1 Molecular Geometry

The title compound with formula $\text{C}_2\text{H}_7\text{NS}$ have 11 atoms. A molecule consisting of N atoms has a total of $3N$ degrees of freedom, corresponding to the Cartesian coordinates of each atom in the molecule. In a nonlinear molecule, 3 of these degrees belong to the rotational, 3 of these degrees belong to the translational motions of the molecule and so the remaining corresponds to its vibrational motions. The net number of the vibrational modes is $3N-6$. Therefore, for the title compound, three Cartesian displacements of 11 atoms provide 27 normal vibration modes. The molecular structure of the molecule is shown in Fig.1.

Fig.1. Molecular structure of the title compound

3.2 Topology analyses

3.2.1 Frontier Molecular Orbitals

The HOMO and LUMO energy gap can be used to explain the molecular chemical stability and chemical reactivity of the molecules. Frontier molecular orbital theory is an application of Molecular orbital theory describing the HOMO [highest Occupied Molecular Orbital] and LUMO [Lowest Unoccupied Molecular Orbital] interactions. In the present compound, the band energy gap between the ground state HOMO (6.55196eV) and the first excitation state LUMO is (0.28191eV) and the value of energy gap is $\Delta E = 6.27005\text{eV}$ [9]. HOMO-LUMO energy plot for the title compound is presented in Fig.2.

Global reactivity descriptors are presented in Table 1. The chemical reactivity descriptors of compounds such as electro negativity (χ), chemical potential (μ), hardness (η), softness (S) and electrophilicity index (ω) are evaluated using the following equations given below:

$$\chi = \frac{I+A}{2}$$

$$\mu = -\frac{I+A}{2}$$

$$\eta = \frac{I-A}{2}$$

$$S = \frac{1}{2\eta}$$

$$\omega = \mu^2/2\eta$$

Table 1 Calculated molecular parameters of the title compound

Parameters	B3LYP/6-311+ G(d,p)
SCF energy (a.u.)	-533.43281
Field Independent Dipole moment (Debye)	
μ_x	-1.2222
μ_y	0.3910
μ_z	0.7452
μ_{total}	1.4839
Zero point vibrational energy (kcal/mol)	57.8897
Total thermal energy (kcal/mol)	61.687
Molar heat capacity at const.volume C_v (cal mol ⁻¹ K ⁻¹)	19.536
Total entropy, S (cal mol ⁻¹ K ⁻¹)	76.290
Vibrational Energy (Kcal/Mol)	59.909
Frontier Molecular Orbital Energies (eV)	
E_{HOMO} (eV)	6.55196

E_{LUMO} (eV)	0.28191
$E_{\text{HOMO}} - \text{LUMO}$ gap (eV)	6.27005
Global Reactivity Descriptors (eV)	
Chemical hardness (η)	3.13502
Softness (S)	0.15948
Chemical potential (μ)	-3.41693
Electronegativity (χ)	3.41693
Electrophilicity index (ω)	1.86209

Fig.2. The Frontier Molecular Orbitals of the title compound.

3.2.2 ELF and LOL analysis

The analysis such as HOMO-LUMO plot, ELF, LOL and Fukui Functions figures were performed using Multiwfn 3.7. [10] which is a multifunctional wave function analysis program. The topological analyses of the Electron Localization function (ELF) and Localized orbital locator (LOL) are tools used for performing covalent bonding analysis as they reveal regions of molecular space where the probability of finding an electron pair is high [11-12] and ELF and LOL figures of the title molecule were presented in Fig.3. and Fig.4. and the relief map with projection of Electron localization function is shown in Fig.5. respectively. It can be seen that the covalent regions have high LOL value (red region), the electron depletion regions between valence shell and inner shell are shown by the blue circles around nuclei. The core regions are characterized by circular localization domains with high (≈ 1) values of electron localization (red) whilst the chemical bonds C-N and C-S are described by irregular localization domains (orange) with smaller values of electron localization (0.8-0.9). Thus both bonds have a covalent character and exhibit high electron localization, typical for shared electron (covalent) bonding. From ELF map, the regions around C3, C4, N2, were found to have lesser value where electrons are expected to be delocalized whereas the regions around hydrogen atoms have comparatively larger values indicating bonding and non-bonding localized electron. So, a large ELF or LOL value [13-14] in a region indicates high localization of electrons due to the presence of covalent bond, a lone pair of electrons or a nuclear shell in that region. Also it is clear from LOL figure, that red colour intrude into interstitial space between boundary atoms.

Fig.3. ELF colour filled map of the title compound

Fig.4. LOL colour filled map of the title compound

Fig.5. Relief map with projection of Electron localization function of the title compound.

3.2.3 Molecular electrostatic potential (MESP) analysis

To investigate reactive sites for electrophilic and nucleophilic attack, the regions of the MEP for the title compound was composed at DFT calculation using the optimized geometry at the B3LYP/6-311 +G(d,p). The different colours on MEP surface represent different values of the electrostatic potential. The potential increases from the least to the most negative according to the following order: blue<green<yellow<red [15-17]. The title compound has a color scale that indicates the positive and negative value reported in Fig.6. From this surface, we can interpret that the most residing areas of electron density (denoted by more red areas) and least electron density residing areas (denoted by deep blue areas). The color code of the map was found to be in the range -3.885×10^{-2} (deepest red color has negative extreme) to 3.885×10^{-2} (deepest blue color has positive extreme). The highest negative potential with red region is visible over the regions N2 of NH₂ group and on Sulfur attached to hydrogen indicating the potential sites for the electrophilic attack. The yellowish blob reflects the less negative potential visible on S₁ attached to hydrogen atom. A more positive charge is localized near the hydrogen atoms connected to N₂ and less on hydrogen atom connected to S₁ atom that indicates the possible sites for nucleophilic attack.

Fig.6.. Molecular Electrostatic Potential of the title compound

Fig.7. Contour map of Molecular Electrostatic potential for the title compound .

In order to examine MEP contour map, multiwfn program was used and shown in Fig.7. It is clear from the contour map that N₂ and S₁ atoms are negatively charged because the local vdW surface is close to N₂ and S₁ atoms and these have largely intersected solid contour lines [18]. This point can be further verified from Hirshfeld atomic charges for the title compound listed in Table 2.

Table 2. Hirshfeld atomic charges of the title compound

Element Name	Atomic charge
S ₁	-0.087886
N ₂	-0.204987
C ₃	-0.009113
C ₄	-0.048221
H ₅	0.033000
H ₆	0.017449
H ₇	0.030874
H ₈	0.033798
H ₉	0.092878
H ₁₀	0.095661
H ₁₁	0.045748

3.2.4 Condensed FUKUI function

The Fukui function describes the electron density after adding or removing some amount of electrons. R.G.Parr and W.Yang [19] reported condensed Fukui function and frontier function. The local reactivity descriptor like Fukui function indicates the preferred regions where a molecule will alter its density or indicates its natural tendency to deform at a given position on accepting or donating electron HUMO or LUMO [20]. In order to find the chemical reactivity and selectivity of the specific atomic site in a molecule, condensed Fukui function and local softness are used [21-22]. The Fukui functions at the atom k result to be:

$$f_k^\alpha = \sum_{v=k} \left[|C_{v\alpha}|^2 + \sum_{x \neq \mu} C_{x\alpha}^* C_{v\alpha} S_{xv} \right]$$

where $C_{v\alpha}$ are the molecular frontier orbitals coefficients and S_{xv} are the atomic orbital overlap matrix elements

$$f_k^- = \sum_{v \neq k} \left[|C_{vH}|^2 + \sum_{x \neq \mu} C_{xH}^* C_{vH} S_{xv} \right] \text{ [for HOMO electrophilic attack]}$$

$$f_k^+ = \sum_{v \neq k} \left[|C_{vL}|^2 + \sum_{x \neq \mu} C_{xL}^* C_{vL} S_{xv} \right] \text{ [for LUMO Nucleophilic attack]}$$

$$f_k^0 = \frac{1}{2} (f_k^+ + f_k^-) \text{ [for radical attack]}$$

The sub-indexes "H" and "L" refers to HOMO and LUMO orbitals. When a molecule gains electrons, it has the reactivity site of electrophilic attack f_k^- , when the molecule losses electrons, it has reactivity site for nucleophilic attack f_k^+ , and when the molecule has neutral electrons, they are in radical attack. Local electrophilicity, Local Nucleophilicity, Hardness and second order Fukui functions are called Dual-Descriptor Δf_r and by using finite difference approximation [23-24], it can be defined as:

$$W_k^+ = W f_k^+ \quad \text{For local Electrophilicity}$$

$$W_k^- = W f_k^- \quad \text{For local Nucleophilicity}$$

$$\eta_k = \epsilon_L f_k^+ - \epsilon_H f_k^- \quad \text{For local Hardness}$$

$$\Delta f_r = |(f_r^+ - f_r^-)| \quad \text{For dual descriptor}$$

Table 3. Condensed Fukui Functions for the title compound

Atom	Atomic Number	HOMO Electrophilic attack	LUMO Nucleophilic attack	Radical attack	Dual-Descriptor	Hardness	Local electrophilic	Local nucleophilic
N	Z	f_k^-	f_k^+	f_0	Δf_r	(au)	$W_k^-(\text{eV})$	$W_k^+(\text{eV})$
S ₁	16	0.9669	0.4023	0.6846	-0.5646	0.3067	0.0601	0.0250
N ₂	7	0.0001	0.0027	0.0014	0.0026	0.0005	0.0000	0.0002
C ₃	6	0.0003	0.0837	0.0420	0.0834	0.0137	0.0000	0.0052
C ₄	6	0.0301	0.5023	0.2662	0.4722	0.0892	0.0019	0.0312

H ₅	1	0.0003	0.0002	0.0003	0.0000	0.0001	0.0000	0.0000
H ₆	1	0.0003	0.0002	0.0002	-0.0001	0.0001	0.0000	0.0000
H ₇	1	0.0010	0.0016	0.0013	0.0006	0.0005	0.0001	0.0001
H ₈	1	0.0010	0.0016	0.0013	0.0006	0.0005	0.0001	0.0001
H ₉	1	0.0000	0.0001	0.0001	0.0001	0.0000	0.0000	0.0000
H ₁₀	1	0.0000	0.0004	0.0002	0.0004	0.0001	0.0000	0.0000
H ₁₁	1	0.0000	0.0048	0.0024	0.0048	0.0008	0.0000	0.0003

The values of local descriptors are evaluated by Frontier Molecular Orbitals for the selected compound and listed in Table 3 and the plot Fukui function for maximum tenancy of electrophilic, radical attack and dual descriptor were shown in Fig.8. The individual atoms are compared to maximum electrophilic attack ($f_k^- = 0.9669$ eV), Radical attack ($f_k^+ = 0.4023$ eV), Dual descriptor ($\Delta f_r = -0.5646$ eV), Hardness (0.3067 au) and Local electrophilic ($W_k^- = 0.0601$ eV) Local nucleophilic ($W_k^+ = 0.025$ eV) for sulfur atom of the title compound.

4. NBO -NLMO and NHO Analysis

The NBOs are one of the sequences of natural localised orbital sets including natural atomic orbitals (NAO), Natural hybrid orbital (NHO) natural bonding orbitals (NBO) and natural localized molecular orbitals (NLMO). These natural localized sets are intermediate one between basis atomic orbitals (AO) and molecular orbitals (MO):

Atomic orbital $\rightarrow$ NAO $\rightarrow$ NHO $\rightarrow$ NBO $\rightarrow$ NLMO $\rightarrow$ Molecular orbital

of the system. The intramolecular hyper conjugative interaction of the bonding σ (C3-H5) to anti-bonding σ^* (N2-H9) leading to stabilization energy of 3.08Kcal/mol, σ (S1-C4) to anti-bonding σ^* (N2-C3) leading to stabilization energy of 3.05Kcal/mol, LP S1 to anti-bonding σ^* (C4-H7)leading to stabilization energy of 4.12Kcal/mol with increasing electron density, LP N1 to anti-bonding σ^* (C3-H6) leading to stabilization energy of 7.20 Kcal/mol with increasing electron density as shown in Table 4.

Table 4: Second Order perturbation theory of Fock Matrix in NBO basis for the title compound

Donor (i)	Type	ED/e	Acceptor (j)	Type	ED/e	E(2) ^a (Kcal/mol)	E(j)- E(i) ^b (a.u)	F(i,j) ^c (a.u)
S1-C4	σ	1.98633	N2-C3	σ^*	0.01001	3.05	0.93	0.048
S1-H11	σ	1.99023	C3-C4	σ^*	0.01778	1.36	0.91	0.031
N2 - C 3	σ	1.99085	S1 - C 4	σ^*	0.01322	2.41	0.87	0.041
N2-H9	σ	1.99076	C3-H5	σ^*	0.01716	1.99	1.01	0.040
N2-H10	σ	1.98902	C3-C4	σ^*	0.01778	2.21	0.99	0.042
N2-H10	σ	1.98902	C3-H5	σ^*	0.01716	0.74	1.01	0.024
C3-C4	σ	1.98874	N2-H10	σ^*	0.00540	1.79	1.06	0.039
C3-H5	σ	1.98033	N2-H9	σ^*	0.00808	3.08	0.93	0.048
C3-H5	σ	1.98033	C4-H7	σ^*	0.02299	2.72	0.89	0.044
C3-H6	σ	1.98758	C4-H8	σ^*	0.02084	2.49	0.90	0.042
C4-H7	σ	1.98696	C3-H5	σ^*	0.01716	2.38	0.90	0.041
C4-H8	σ	1.98698	C3-H6	σ^*	0.03243	2.45	0.89	0.042
LP S1	σ	1.99301	C4-H8	σ^*	0.02084	0.50	1.03	0.020
LP S1	π	1.97238	C4-H7	σ^*	0.02299	4.12	0.63	0.046
LP S1	π	1.97238	C4-H8	σ^*	0.02084	3.39	0.64	0.042
LP N2	σ	1.95737	S1-C4	σ^*	0.01322	0.85	0.46	0.018
LP N2	σ	1.95737	C3-C4	σ^*	0.01778	1.73	0.69	0.031
LP N2	σ	1.95737	C3-H5	σ^*	0.01716	0.63	0.70	0.019
LP N2	σ	1.95737	C3-H6	σ^*	0.03243	7.20	0.69	0.063

a E⁽²⁾ means energy of hyper conjugative interaction (stabilization energy).

b Energy difference between donor and acceptor i and j NBO orbitals.

c F(i,j) is the Fock matrix element between i and j NBO orbitals.

The Natural localized molecular orbital (NLMO) analysis of the title compound shows the electron overlap implying NLMO is slightly delocalized NBO [28] as listed in Table 5

$$BD(1) = \sigma CH = 0.7815(sp^{3.02})_C + 0.6239(sp^{0.00})_H$$

$$BD^*(1) = \sigma NC = 0.6395(sp^{2.08})_N + 0.6239(sp^{2.98})_C$$

The NBO orbital output σ (C₄-H₈) orbital with 1.98698 electron occupancy has 61.07% C₄ character in sp^{3.02} hybrid, polarization coefficient 0.7815 (75.05 % p- character, 24.89% s-character) and has 38.93% H₈ character in sp^{0.00} hybrid, polarization coefficient 0.6239 (0.04% p-character, 99.96 s-character). The related antibond output σ^* (N₂-C₃) orbital with 0.01001 electron occupancy is 2-center bond, has 40.90 % N₂ character in sp^{2.08} hybrid, polarization coefficient 0.6395 (67. 54 % p- character, 32.40% s-character) and has 59.10% H₈ character in sp^{2.98} hybrid, polarization coefficient -0.7687 (74.79% p-character, 25.09 s-character).

Table 5 :NLMO analysis of the title compound

NLMO	Occupancy	Polarization coefficient	NBO Bond (A-B)	Percent of the NLMO each atom	Hybrid composition ratio of the NAOs	S (%)	P (%)
1	1.98633	0.6952*	$\sigma(\text{S1-C4})$	48.33%	S1sp(5.32)	15.73	83.76
		0.7188*		51.67%	C4sp(3.79)	20.86	78.98
5	1.98902	0.8243*	$\sigma(\text{N2-H10})$	67.95%	N2 sp(3.14)	24.13	75.78
		0.5661*		32.05%	H10 sp(0.00)	99.94	0.06
7	1.98033	0.7735*	$\sigma(\text{C3-H5})$	59.82%	C3sp(3.38)	22.83	77.10
		0.6338*		40.18%	H5sp(0.00)	99.96	0.04
10	1.98698	0.7815*	$\sigma(\text{C4-H8})$	61.07%	C4 sp(3.02)	24.89	75.05
		0.6239*		38.93%	H8sp(0.00)	99.96	0.04
19	1.99301	-	LP(1)S1	-	S1Sp(0.41)	70.87	29.12
20	1.97238	-	LP(2)S1	-	S1sp(99.99)	0.02	99.94
21	1.95737	-	LP(1)N2	-	N2sp(4.18)	19.29	80.66
129	0.01322	0.7188*	$\sigma^*(\text{S1-C4})$	51.67%	S1sp(5.32)	15.73	83.76
		-0.6952*		48.38%	C4sp(3.79)	20.86	78.98
130	0.00489	0.6616*	$\sigma^*(\text{S1-H11})$	43.77%	S1sp(6.30)	13.62	85.85
		-0.7499*		56.23%	H11sp(0.00)	99.68	0.32
131	0.01001	0.6395*	$\sigma^*(\text{N2-C3})$	40.90%	N2sp(2.08)	32.40	67.54
		-0.7687*		59.10%	C3sp(2.98)	25.09	74.79
134	0.01778	0.7121*	$\sigma^*(\text{C3-C4})$	50.71%	C3sp(2.48)	28.70	71.25
		-0.7020*		49.29%	C4sp(2.34)	29.96	70.00
138	0.02084	0.6239*	$\sigma^*(\text{C4-H8})$	38.93%	C4sp(3.02)	24.89	75.05
		-0.7815*		61.07%	H8sp(0.00)	99.96	0.04

Table 6. NHO analysis for the title compound

NBO		Line of Centers		Hybrid 1			Hybrid 2		
		Theta	Phi	Theta	Phi	Dev	Theta	Phi	Dev
1	$\sigma(\text{S1-C4})$	92.9	154.7	92.5	156.1	1.4	87.4	336.6	1.9
2	$\sigma(\text{S1-H11})$	97.7	57.8	97.4	53.0	4.8	-----	-----	-----
3	$\sigma(\text{N2-C3})$	88.3	334.8	-----	----	----	89.2	155.4	2.5
4	$\sigma(\text{N2-H9})$	29.4	117.2	30.7	115.8	1.5	-----	-----	-----
5	$\sigma(\text{N2-H10})$	100.8	223.5	101.9	222.5	1.5	-----	-----	-----
6	$\sigma(\text{C3-C4})$	92.1	45.2	-----	-----	----	87.6	227.9	2.7
8	$\sigma(\text{C3-H6})$	36.3	284.4	34.6	281.2	2.6	-----	-----	-----
9	$\sigma(\text{C3-H7})$	39.7	99.5	38.7	98.5	1.2	-----	-----	-----
10	$\sigma(\text{C3-H8})$	148.6	99.5	149.5	96.3	1.9	-----	-----	-----
19	LP(1)S1	-----	-----	80.5	288.2	-----	-----	-----	-----
20	LP(2)S1	-----	-----	171.0	264.5	-----	-----	-----	-----
21	LP(1)N2	-----	-----	136.2	92.1	-----	-----	-----	-----

The angular properties of the natural hybrid orbitals (NHO) are directions of a hybrid specified in terms of the polar (θ) and azimuthal (ϕ) angles of the vector describing its p-component. The hybrid direction is compared with the direction of the line of centers between the two nuclei to determine the bending of the bond and expressed as the deviation angle (Dev) between these two directions. The NHO information is often useful in anticipating the direction of geometry changes resulting from geometry optimization. For the title compound, with reference to the Table -- , the NHO of the $\sigma(\text{S1-H11})$ is bent away from the line of centers polar angle 97.7, azimuthal angle 57.8 by hybrid (1) polar angle (θ) 97.4, azimuthal angle (ϕ) 53.0 and deviation angle (Dev) 4.8 degree [29]. The direction of geometry changes due to the geometrical optimization can be expected using the data obtained from Table 6.

5. Conclusion

The optimization of structure geometry was done by DFT/B3LYP functional which confirms the molecular geometry. The significant difference in HOMO-LUMO energy gap supports the charge transfer within the molecule. ELF studies showed a stronger chemical bonding between CH bonds due to the overlap of sp orbital of carbon with s orbital of hydrogen which is electronically more stable. Condensed Fukui function and MESP map were shown to reveal the negative and positive regions of the molecule. MESP analysis identifies nitrogen of NH₂ group to be more sensitive towards the electrophilic attack. The hyperconjugative interactions in NBO analysis support intramolecular nature of the hydrogen bonding and charge transfer interactions where electron donating from LP N2 $\rightarrow \sigma^*$ (C3-H6) showed the maximum stabilization energy of 7.20 Kcal/mol. NBO, NLMO and NHO analysis were carried out to comprehend the angular properties, electron occupancy and the stability of the title compound from the hyper conjugative interaction and charge delocalization. The polar (θ) and azimuthal (ϕ) angles of the vector form from the nucleus along with the deviation angle were used to specify the direction of a hybrid.

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