A QUANTUM CHEMICAL INVESTIGATION OF N^1-SUBSTITUTED 1,2,4-TRIAZOLE

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Abstract. *The molecular conformations and electronic properties of a set of five N^1-(o/p-substituted phenyl)aminomethyl-1,2,4-triazole derivatives (PhAMT) were investigated by two semiempirical methods: AM1 and PM3. Characteristic bond lengths (N_1-C_2, C_2-H_6, C_2-N_3, N_3-N_4, N_4-C_5, C_5-H_7 and N_1 - C_5), angles (N_1-C_2-N_3, C_2-N_3-N_4, N_3-N_4-C_5, N_4-C_5-N_1 and C_5-N_1-C_2) and atomic charges (N_1, C_2, N_3, N_4, C_5, H_6 and H_7) for 1,2,4-triazole core were calculated and discussed in accordance with literature data for similar 1,2,4-triazole compounds. The E_{HOMO} and E_{LUMO} values, total energies, the heats of formation and dipole moments values were calculated, as well. The discussion was performed in accordance with the type and position of a substituent present in the aromatic core.*

Key words: *AM1, PM3, atomic charge, bond length, dipole moment, EHOMO, ELUMO, heat of formation, 1,2,4-triazole derivatives*

1. INTRODUCTION

Among different heterocyclic systems, 1,2,4-triazoles belong to a significant class of heterocyclic compounds due to their diverse biological properties. [1]. Triazole compounds in their structure contain five member rings with three nitrogen atoms and they have different structural formulas. It is well known that the parent 1,2,4-triazole (1H form) is in tautomeric equilibrium with the 1,2,4-triazole (4H form) [2].

According to the latest literature, five membered heterocycles such as 1,2, 4-triazole ring are significant units in drug design [3]. Triazoles form is an important cluster among the heterocyclic compounds which possess a wide range of biological applications. The 1,2,4-triazole derivatives possess important pharmacological activities such as antifungal and antiviral [4]. The examples of antifungal drugs are itraconazole, fluconazole, ravuconazole, voriconazole and posaconazole [5]. Furthermore, 1,2,4-triazole derivatives are reported as insecticides, antiasthmatics, anticonvulsants, antidepressants, anti-inflammatory, insecticidal and plant growth regulators [6].

This paper represents a semiempirical quantum chemical investigation of chosen N^1-substituted-1,2,4-triazole derivatives PhAMT (1-5) previously synthesized and investigated [7]. The molecular conformations and electronic properties of investigated molecules were studied by AM1 and PM3 semiempirical methods. The total energies, heats of formation, dipole moments, geometric parameters,

ionization potential, full atomic charges, E_{HOMO} and E_{LUMO} values were calculated and discussed.

2. EXPERIMENTAL

2.1. Materials and methods

N^1-(o/p-substituted phenyl)aminomethyl-1,2,4-triazole derivatives (PhAMT 1–5), (See Table 1), used in this study were previously synthesized and reported elsewhere [7].

2.2. Quantum chemical investigation

Theoretical calculations were performed by using HYPERCHEM program [8]. The geometries of N^1-(o/p-substituted phenyl)aminomethyl-1,2,4-triazole derivatives (PhAMT 1–5) were fully optimized using AM1 and PM3 semiempirical method. All the structures were optimized to a gradient norm of < 0.1.

AM1 (Austin model 1) AM1 is a semiempirical method based on the neglect of differential diatomic overlap integral approximation. Specifically, it is a generalization of the modified neglect of diatomic differential overlap approximation. AM1 was developed by Michael Dewar and coworkers reported in 1985 [9].

PM3 (parameterized model number 3) PM3 is another semiempirical method based on the neglect of differential diatomic overlap integral approximation. The PM3 method uses the same formalism and equations such as the AM1 method. The only

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differences are: (a) PM3 uses two Gaussian functions for the core repulsion function instead of the variable number used by AM1 (which uses between one and four Gaussians per element); (b) the numerical values of the parameters are different. The other differences lie in the philosophy and the methodology used during the parameterization: whereas AM1 takes some of the parameter values from spectroscopic measurements, PM3 treats them as optimized values. The PM3 method was developed by Stewart and first reported in 1989 [10].

Table 1. Structure of investigated N^1-(o/*p*-substituted phenyl)aminomethyl-1,2,4-triazole derivatives (PhAMT 1 – PhAMT 5)

3. RESULTS AND DISCUSSION

The study of the geometry of complex system such as investigated ones (PhAMT 1-5) is important because of the possible usefulness of such information as an aid to the understanding of the mode of action of PhAMT:

○ as acid or as base and
○ co-coordinative species

The optimized geometrical parameters of selected N^1-(o/*p*-substituted phenyl)aminomethyl-1,2,4-triazole derivatives (PhAMT 1-5) such as: bond length, angles and atomic charge are presented in Tables 2 and 3.

Table 2. Selected geometrical parameters: bond length, angle and of atomic charge of PhAMT 1-5 calculated by AM1 semiempirical method

AM1	PhAMT 1	PhAMT 2	PhAMT 3	PhAMT 4	PhAMT 5
Length [Å]					
N_1-C_2	1.4120	1.4114	1.4082	1.4107	1.4089
C_2-N_3	1.3593	1.3599	1.3604	1.3604	1.3620
N_3-N_4	1.3486	1.3481	1.3444	1.3475	1.3438
N_4-C_5	1.4168	1.4160	1.4122	1.4152	1.4142
N_1 - C_5	1.3452	1.3458	1.3487	1.3405	1.3480
C_2-H_6	1.0945	1.0949	1.0942	1.0949	1.0944
C_5-H_7	1.0947	1.0948	1.0938	1.0947	1.0937
Angle [deg]					
N_1-C_2-N_3	112.99°	112.98°	112.88°	112.98°	112.92°
C_2-N_3-N_4	104.62°	104.63°	104.78°	104.62°	104.83°
N_3-N_4-C_5	109.57°	109.57°	109.53°	109.60°	109.45°
N_4-C_5-N_1	109.18°	109.20°	109.35°	109.19°	109.4°
C_5-N_1-C_2	103.58°	103.56°	103.43°	103.55°	103.38°
Atomic charge					
N_1	-0.154	-0.155	-0.159	-0.156	-0.155
C_2	-0.151	-0.149	-0.157	-0.152	-0.163
N_3	-0.08	-0.091	-0.099	-0.091	-0.079
N_4	-0.187	-0.184	-0.199	-0.182	-0.199
C_5	-0.067	-0.066	-0.080	-0.068	-0.096
H_6	0.212	0.212	0.208	0.211	0.208
H_7	0.212	0.212	0.206	0.212	0.240

Table 3. Selected geometrical parameters: length, angle and of atomic charge of PhAMT 1-5 calculated by PM3 semiempirical method

PM3	PhAMT 1	PhAMT 2	PhAMT 3	PhAMT 4	PhAMT 5
Length [Å]					
N_1-C_2	1.3927	1.3927	1.3923	1.3919	1.3932
C_2-N_3	1.3447	1.3447	1.3453	1.3453	1.3441
N_3-N_4	1.3755	1.3762	1.3756	1.3760	1.3747
N_4-C_5	1.3907	1.3904	1.3906	1.3896	1.3920
N_1-C_5	1.3477	1.3478	1.3474	1.3485	1.3466
C_2-H_6	1.0922	1.0921	1.0923	1.0922	1.0924
C_5-H_7	1.0934	1.0935	1.0934	1.0936	1.0933
Angle [deg]					
N_1-C_2-N_3	109.21°	109.21°	09.19°	109.22°	109.16°
C_2-N_3-N_4	106.40°	106.39°	106.44°	106.37°	106.50°
N_3-N_4-C_5	109.65°	109.65°	109.60°	109.67°	109.57°
N_4-C_5-N_1	106.30°	106.29°	106.33°	106.30°	106.31°
C_5-N_1-C_2	108.43°	108.44°	108.44°	108.42°	108.45°
Atomic charge					
N_1	-0.169	-0.171	-0.169	-0.174	-0.165
C_2	-0.073	-0.071	-0.072	-0.072	-0.076
N_3	-0.239	-0.244	-0.239	-0.247	-0.227
N_4	-0.2167	-0.219	-0.179	-0.222	-0.181
C_5	-0.174	-0.170	-0.171	-0.168	-0.183
H_6	0.162	0.162	0.162	0.161	0.163
H_7	0.167	0.169	0.169	0.170	0.169

3.1. Characteristic bond length in 1,2,4-triazole ring

Bond length characteristic for 1,2,4-triazole moiety in PhAMT (1-5) molecule are: N_1-C_2, C_2-H_6, C_2-N_3, N_3-N_4, N_4-C_5, C_5-H_7 and N_1 - C_5. The obtained data are presented in Tables 2 and 3.

Calculated bond lengths values are comparable with the corresponding experimental ones for unsubstituted 1H-1,2,4-triazole [11].

It can be noticed (See Tables 2 and 3) that the bond lengths of the N-N bond in 1,2,4-triazole core calculated with: *i)* AM1 method range from 1.3438 ÷ 1.3486 Å; *ii)* PM3 method range from 1.3747 ÷ 1.3762 Å, which is shorter compared with the normal N-N (single) bond (1.45Å), but longer than the N=N (double) bond (1.25 Å) [12]. The values calculated by AM1 are in good agreement with the same distance in 1,2,4-triazole (1.350) according to the literature [13].

The C-N bonds in PhAMT (1-5) can be classified according to the bond type observed: N_1 - C_2 / N_4-C_5 and C_2-N_3 / N_1 – C_5.

The single C – N covalent bond (N_1 - C_2 / N_4-C_5) can be compared with the corresponding values reported in literature [11] for unsubstituted 1H-1,2,4-triazole:

i) for PhAMT (1-5)
- N_1 - C_2: 1.4083 ÷ 1.4120 Å (AM1) and 1.3919 ÷ 1.3932 Å (PM3);
- N_4-C_5: 1.4122 ÷ 1.4168 Å (AM1) and 1.3896 ÷ 1.3920 Å (PM3).

ii) Literature values for the same distance in 1H-1,2,4-triazole [11]:
- experimental values: 1.348 Å (N_1 - C_2) and 1.377 Å (N_4-C_5);
- calculated with PM3 method: 1.386 Å (N_1 - C_2) and 1.383 Å (N_4-C_5)

iii) typical single C-N bond: 1.47 Å [12]

Second type C = N (double) covalent bond in triazole ring has following values:

i) for PhAMT (1-5)
- C_2-N_3: 1.3593 ÷ 1.3623 Å (AM1) and 1.3441 ÷ 1.3453 Å (PM3);
- N_1 – C_5: 1.3405 ÷ 1.3487 Å (AM1) and 1.3466 ÷ 1.3485 Å (PM3).

ii) Literature values for 1H-1,2,4-triazole [11]:
- C_2-N_3: 1.305 Å (exp.), 1.351 Å (calc.) and
- N_1-C_5: 1.329 Å (exp.), 1.353 Å (calc.)

iii) typical single C=N bond: 1.287 Å [12]

3.2. Characteristic angles in 1,2,4-triazole ring

The optimized geometrical structures of PhAMT (1-5) showed corresponding angle values (Tables 2 and 3):
- N_1-C_2-N_3: 112.88 ÷ 112.99° calculated by AM1 method; 109.16 ÷ 109.22° calculated by PM3 method;
- C_2-N_3-N_4: 104.62 ÷ 104.83° calculated by AM1 method;

Total energies (E_{tot}), the heats of formation (ΔH_f^o), energies of frontier molecular orbitals: the highest occupied (E_{HOMO}) and the lowest unoccupied molecular orbital (E_{LUMO}) and dipole moments μ (in Debyes) of PhAMT (1-5) were calculated. The obtasined values are given in Table 4. In fact, the stability of complex heterocyclic systems such as PhAMT (1-5), depends on the conjugation between the: heterocyclic ring, (in this case 1,2,4-triazole), aminomethyl unit and *o/p* – substituted aromatic rings.
- 106.37 ÷ 160.50° calculated by PM3 method;
- N_3-N_4-C_5: 109.45 ÷ 109.60° calculated by AM1 method; 109.57 ÷ 109.67° calculated by PM3 method;
- N_4-C_5-N_1: 109.18 ÷ 109.40° calculated by AM1 method; 106.29 ÷ 106.33° calculated by PM3 method;
- C_5-N_1-C_2: 103.38 ÷ 103.58° calculated by AM1 method; 108.42 ÷ 108.45° calculated by PM3 method.

According to the literature [11], corresponding angle values calculated for unsubstituted triazole ring are similar for N=C-N (113.80°) in case when both N atom have no H atom. The angle values for C-N-N were 102.70° when central N atom has no H atom and 105.70° for C-N-C angle.

3.3. Characteristic atomic charges in 1,2,4-triazole ring

It is known that atomic charges in the molecule are obviously responsible for electrostatic interactions. Thus, they are often used for the description of the molecular polarity of molecules. Mulliken population analysis is generally used for the calculation of the charge distribution in different molecules because these numerical quantities are easy to calculate. Furthermore, they provide a qualitative understanding not only of the structure but also the reactivity of the molecules.

Table 4. Total energies, heats of formation, semiempirical calculated relative stabilities, E_{HOMO} and E_{LUMO} energies of frontier molecular orbitals, dipol moments for PhAMT (1–5)

	PhAMT 1	PhAMT 2	PhAMT 3	PhAMT 4	PhAMT 5
AM1					
μ [D]	3.237	0.873	2.354	3.112	0.824
E_{HOMO} [eV]	-9.052	-8.912	-8.870	-8.545	-8.455
E_{LUMO} [eV]	-0.441	-0.138	0.132	-0.193	0.084
E_{tot} [kcal/mol]	-66.510	-56.597	-52.364	-67.742	-77.927
ΔH_f [kcal/mol]	29.767	123.895	107.249	144.635	210.886
PM3					
μ [D]	4.101	2.993	2.550	3.960	0.157
E_{HOMO} [eV]	-9.255	-9.186	-8.894	-8.857	-8.643
E_{LUMO} [eV]	-0.748	-0.302	-0.057	-0.399	-0.183
E_{tot} [kcal/mol]	-59.356	-50.864	-46.522	-60.874	-67.623
ΔH_f [kcal/mol]	62.433	89.490	71.416	106.049	139.910

The Mulliken atomic charge of the 1,2,4-triazole core atoms calculated by AM1 and PM3 methods are listed in Tables 2 and 3. The results pointed that:
- AM1: N_4 atom and

○ PM3: N$_3$ atom

in all investigated triazoles were atoms with the highest negative values. In accordance with the negative charge distribution on atoms in the PhAMT (1-5), the N$_4$/N$_3$ was predicted to be the main site of the molecule for the electrophilic attack of hydrogen. Since, both investigated hydrogen atoms (H6 and H7) had similar atomic charge values, they had the same possibility of carrying out the deprotonation process in both cases: C2 – H6 and C5 – H7.

Total energies (E_{tot}), the heats of formation (ΔH_f^o), energies of frontier molecular orbitals: the highest occupied (E_{HOMO}) and the lowest unoccupied molecular orbital (E_{LUMO}) and dipole moments μ (in Debyes) of PhAMT (1-5) were calculated (See Table 4). In fact, the stability of complex heterocyclic systems, such as PhAMT (1-5) depends on the conjugation between the heterocyclic ring, (in this case 1,2,4-triazole), aminomethyl unit and *o/p* - substituted aromatic rings.

3.4. Dipole moment (μ)

The dipole moment of the molecule is the most widely used quantity to describe their polarity. The size of the dipole moment calculated by both semiempirical methods (AM1 and PM3) depends on the type and position (*o-/p-*) of substituent associated with the aminomethyl-phenyl unit. PhAMT 1, with *o*-substituted –COOH group relative to the benzene core had the highest dipole moment: 3.237 D (AM1) and 4.101 D (PM3). The lowest dipole moment had PhAMT 5 in which the second triazole nucleus is divided from benzene core by an additional aminomethyl bridge: 0.824 D (AM1) and 0.157 D (PM3) (Table 4).

3.5. Total energies (E_{tot})

Knowing that the total energy of a system is composed of internal, potential and kinetic energy, the total energy calculated by quantum chemical methods (AM1 and PM3) is also an important parameter for the understanding of the structure and reactivity of the investigated triazole molecules. PhAMT 5 had the highest negative values for total energies calculated by AM1 and PM3 method (Table 4). Triazole with *p*-substituted moderately activating group such as –CH$_3$ (PhAMT 3) had the lowest negative total energies values (Table 4).

3.6. Molecular orbital energies

The frontier orbital: E_{HOMO} and E_{LUMO} (highest/lowest occupied molecular orbital energy) are very known quantum chemical parameters. They determine the way the molecule interacts with other species in chemical reactions and play important role in the optical and electrical properties [12]. According to the frontier molecular orbital theory, the highest occupied molecular orbital is the orbital that could act as an electron donor, while the lowest occupied molecular orbital could act as the electron acceptor. The formation of a transition state is due to an interaction between the frontiers orbital of reactants. Calculated E_{HOMO} and E_{LUMO} values of invesigated triazoles are presented in Table 4. The HOMO–LUMO gap (E_{gap} = E_{HOMO} - E_{LUMO}) is an important stability

indicator. The larger values of E_{gap} imply high stability of the molecule in chemical reactions [14], and the smaller values indicate that the molecule is more probable to give higher inhibition efficiency.

The E_{HOMO} is directly related to the ionization potential (IP = - E_{HOMO}) and the energy of the LUMO is directly related to the electron affinity. IP of PhAMT 1 had the higher values compared with the rest of compounds: 9.0520 calculated by AM1 method and 9.2553 calculated by PM3 method. Those values were lower than those reported in the literature for 1,2,4-triazole. According to the literature, the experimental IP value of 1,2,4-triazole molecule was 10.00 eV, while calculated IP value using AM1 and PM3 methods was 10.27 and 10.396 eV, respectively [15].

3.7. Heats of formation (ΔH$_f^o$).

Heat of formation (HOF) is one of the most crucial thermodynamic quantities. It is required to estimate the amount of energy released or absorbed in a chemical reaction in order to calculate other thermodynamic functions and, what is more important, to assess the stability of a molecule [16]. The heats of formations (*ΔH$_f^o$*) for selected triazole compounds were also calculated using AM1 and PM3 semiempirical methods (Table 4). It can be clearly seen from the Table 4 that the *ΔH$_f^o$* increased according to the following order in both cases:

PhAMT 5 > PhAMT 4 > PhAMT 2 > PhAMT 3 > PhAMT 1.

4. CONCLUSION

In the most cases, quantum chemical investigations can be used in structure elucidation of organic molecules and this kind of calculation should be performed as a prediction of possible synthesis and stability of the predictive product. The subject of this investigation was a set of five N^1-(o/*p*-substituted phenyl)aminomethyl-1,2,4-triazole derivatives PhAMT (1–5). Characteristic bond lengths, angles and atomic charges were calculated by AM1 and PM3 methods and compared with literature data for compounds with same heterocyclic core. All compared data were in a good agreement with each other. E_{HOMO} and E_{LUMO} values, total energies (E_{tot}), the heats of formation (ΔH_f^o), and dipole moments (μ) for investigated PhAMT (1–5) were also calculated and disscused in accordance with the structure of substituted triazoles. All the calculated data were useful not only for the characterization of the triazole molecules, but they also could help in understanding the type of action of PhAMT (1–5) especially in acid/base reactions and in coordinative chemistry. This information also could be helpful for fundamental researches in heterocyclic chemistry and biology, and also for further application of investigated compounds in pharmacy and other industries, as well.

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