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Original Research Paper Chemistry

SYNTHESIS AND COMPUTATIONAL STUDIES OF PYRIDYLMETHYL-(*1H*)-TETRAZOLES

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ABSTRACT A convenient procedure for the synthesis of 4-pyridylmethyl-*1H*-tetrazole has been developed from 4-methylpyridine by brominating with NBS, cyanation than followed by treated with sodium azide in the presence of [Bmim]BF_4 ionic liquid. In this we have studied structure, thermal, electro static potential, bond lengths and bond angles of 4-Pyridylmethyltetrazole. And also we have studied frontier orbital HOMO-LUMO surfaces, Molecular electrostatic potential surfaces. A computational study was conducted by Argus Lab 4.0.1 to obtain the most active conformation and to analyze its excited-state properties.

KEYWORDS : N-Bromosuccinamide, tetrazole, sodium azide, HOMO, LUMO

INTRODUCTION

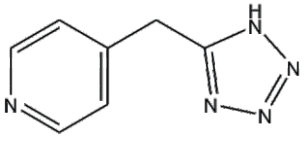
Tetrazole compounds have found use in pharmaceuticals as lipophilic spacers [1] and carboxylic acid surrogates [2] in specialty explosives and photography and information recording systems [3], not to mention as precursors to a variety of nitrogen containing heterocycles[4]. These derivates are well known as compounds with a high level of biological activity [5] and also regarded as biologically equivalent to carboxylic acid group [6]. Some of heterocyclic compounds containing pyridine rings are shows pharmacological properties such as antimicrobial[7,8], anticancer [9] anticonvulsant [10], antiviral [11], anti-HIV[12], antifungal and anti-mycobacterial activities [13].

Though the above mentioned studies have been carried out on tetrazole derivatives but no computational studies have been made so far on conformational analysis (geometry optimization) and excited-state properties by modern quantum chemical methods. The present work describes the synthesis and computer aided geometry optimization (active conformation) and calculation of excited state properties of 4-pyridyl methyl tetrazole by Argus Lab 4.0.1 software. [14] Argus Lab is molecular modeling software and the latest version 4.0.1 is capable of performing various molecular calculations such as geometry optimization, molecular structure visualization, etc to provide users with molecular building analyses.

MATERIALS AND METHODS

Melting points were uncorrected. Infra Red spectra were obtained by using a Bruker WM-4(X) spectrometer (577 model). ^{1}H NMR (400MHz) and ^{13}C NMR (100MHz) spectra were recorded on a Bruker WM-400 spectrophotometer in DMSO-$_6$ with Tetra Methyl Silane as reference. Mass spectra (ESI) were carried out on a JEOL SX-102 spectrophotometer. Elemental analysis was done by the Carlo Erba EA 1108 automatic elemental analyzer

The structure of 4-pyridyl methyl tetrazole was drawn and constructed using window based program of Argus Lab and ACD Lab Chem Sketch software. Conformational analysis (geometry optimization) of 4-pyridyl methyl tetrazole was carried out using PM3 semi-empirical QM parameterization according to Hartree-Fock calculation method by Argus Lab 4.0.1 software. Many of these kinds of surfaces are shown and described in this work. The electronic excited-state calculations were carried out by ZINDO semi-empirical method which is parameterized for low energy excited-states of organic molecules.



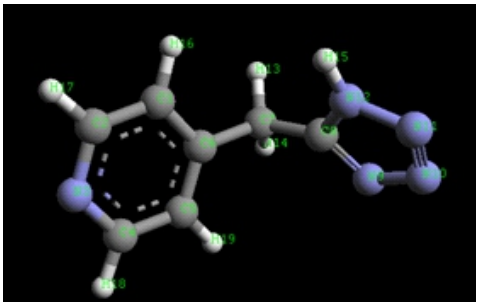


Fig. 1: Perspective view of 4-pyridyl methyltetrazole in generated by ACD Lab Chem Sketch

Active conformation of 4-pyridyl methyl tetrazole with labeled atoms is illustrated in **Figure 1** by Argus Lab software. **Figure 2** shows the electron density clouds of 4-(1H-tetrazol-5-yl) methyl pyridine by ACD Labs 3D viewer software. Atomic coordinates are given in **Table 1**. **Tables 2** and **3** represent the bond angles and bond lengths respectively calculated from geometry optimization of 4-(1H-tetrazol-5-yl)methylpyridine. **Figure 3** illustrates the frontier molecular orbitals i.e. Highest energy occupied molecular orbital (HOMO) and the lowest unoccupied (LUMO) molecular orbital.

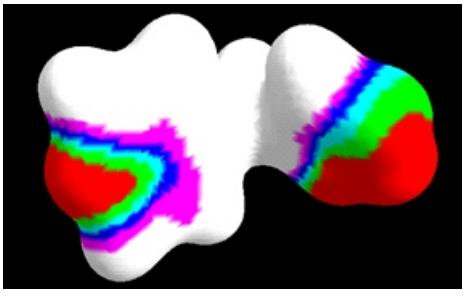


Figure 2: Electrostatic potential (ESP) mapped Electron density on 4-(1H-tetrazol-5-yl) Methyl pyridine

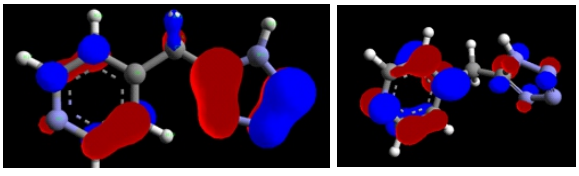


Figure 3: HOMO and LUMO of 4-(1H-tetrazol-5-yl) methylpyridine(4):

RESULTS AND DISCUSSION:

The synthetic scheme was depicted in **Scheme 1**. The starting compound 2-bromo methyl pyridine (2) was prepared from 4-methyl pyridine (1) by reacted with NBS under microwave conditions. The compound (2) is treated with CuCN in DMF solvent to produced 4-pyridyl acetonitrile (3) which is cyclized with sodium azide in the presence of [Bmim]BF_4 ionic liquid [15] at 80 ^{0}C to afford title compounds in good yields.

The active conformation and electron density clouds of 4-pyridyl methyl tetrazole represent the arrangement of electrons around the atom which determines the energy level of 4-pyridyl methyl tetrazole. The geometry convergence map of 4-pyridyl methyl tetrazole clearly shows a decrease in potential energy with the progress of rotation. Among the molecular orbitals, HOMO is a non bonding type while the LUMO is a π molecular orbital. The positive and negative charges are indicated by blue and red color, respectively. LUMO map can provide an idea for nucleophilicity. Argus Lab can also map the electronic properties onto the surface of electron density. **Figure 2** shows the Electrostatic Potential (ESP) of 4-pyridyl methyl tetrazole ground state mapped onto the electron density surface for the ground state rendered as mesh to reveal the underlying structure. The colors are the values of the ESP energy (in red color indicates the enhanced electron density around the oxygen-ends of the molecule representing the most negative regions of the ESP (region of highest stability) for a positive test charge where it would have favorable interaction energy. The best conformation of 4-pyridylmethyltetrazole **(4)** was found to be -54811.7500 kcal/mol which is the minimum potential energy calculated by geometry convergence function by Argus Lab software; performed according to Hartree-Fock calculation method.

Scheme 1:

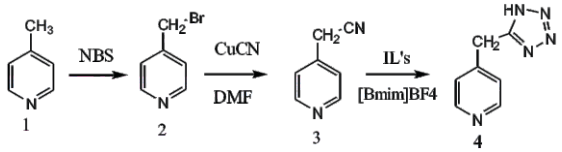


Table -1: Atomic Co ordinates of 4-pyridyl methyl tetrazole (4):

S. No	Atoms	X	Y	Z
1	C	-2.466875	0.678684	0.008326
2	C	-3.655853	-0.035036	0.104784
3	N	-3.632639	-1.408074	0.115240
4	C	-2.447529	-2.096557	0.035374
5	C	-1.247708	-1.402757	-0.061856
6	C	-1.242022	-0.001043	-0.079704
7	C	0.016311	0.802372	-0.213891
8	C	1.282135	0.046831	-0.014453
9	N	1.457094	-1.305007	-0.024691
10	N	2.750847	-1.586893	0.176986
11	N	3.421100	-0.508655	0.313153
12	N	2.556290	0.544637	0.203954
13	H	-0.020684	1.657558	0.495795
14	H	0.024042	1.250486	-1.233220
15	H	2.866610	1.483851	0.278578
16	H	-2.500510	1.7777923	0.002071
17	H	-4.629848	0.479650	0.173493
18	H	-2.467754	-3.200618	0.049626
19	H	-2.551592	-1.943186	-0.112919

Table 2: Bond lengths of 4-pyridyl methyl tetrazole (4):

Sl. No.	Atoms	Bond Lengths	Bond order
1	8C-12N	1.387403	Single bond
2	11C-12N	1.366771	Single bond
3	10C-11N	1.280922	Double bond
4	9C-10N	1.338407	Single bond
5	8C-9N	1.358186	Double bond
6	7C-8C	1.487931	Single bond
7	6C-7C	1.499394	Single bond
8	5C-6C	1.395242	1.50
9	3N-4C	1.353544	1.50
10	2C-3N	1.353531	1.50
11	1C-2C	1.395356	1.50
12	14H-1N	1.095337	Single bond
13	15H-2C	1.096527	Single bond
14	18H-4C	1.096794	Single bond
15	19H-5C	1.096245	Single bond

Table 3: Bond Angles of 4-Pyridyl methyl *(1H)*-tetrazoles (4):

S. No	Atoms	Bond angles	Alternate Bond angles
1	C_2-C_1-C_6	120.000000	222.595017
2	C_2-C_1-H_{16}	120.000000	114.188575
3	C_1-C_2-N_3	120.000000	303.537949
4	C_1-C_2-H_{17}	120.000000	114.188575
5	C_6C_1-H_{16}	120.000000	114.188575
6	C_1-C_6-C_5	120.000000	222.595017
7	C_1-C_6-C_7	120.000000	198.274298
8	N_3-C_2-H_{17}	120.000000	156.569278
9	C_2-N_3-C_4	120.000000	233.893264
10	N_3-C_4-C_5	120.000000	303.537949
11	N_3-C_4-H_{18}	120.000000	156.569278
12	C_5-C_4-H_{18}	120.000000	114.188575
13	C_4-C_5-C_6	120.000000	222.595017
14	C_4-C_5-H_{19}	120.000000	114.188575
15	C_6-C_5-H_{19}	120.000000	114.188575
16	C_5-C_6-C_7	120.000000	198.274298
17	C_6-C_7-C_8	109.470000	226.550294
18	C_6-C_7-H_{13}	109.470000	121.420518
19	C_6-C_7-H_{14}	109.470000	121.420518
20	C_8-C_7-H_{13}	109.470000	121.420518
21	C_8-C_7-H_{14}	109.470000	121.420518
22	C_7-C_8-N_9	120.000000	285.265850
23	C_7-C_8-N_{12}	120.000000	249.648070
24	H_{13}-C_7-H_{14}	109.470000	74.849522
25	N_9-C_8-N_{12}	120.000000	402.764879
26	C_8-N_9-N10	120.000000	315.342899
27	C_8-N_{12}-N_{11}	120.000000	273.709525
28	C_8-N_{12}-H_{15}	120.000000	108.672864
29	N_9-N_{10}-N_{11}	120.000000	471.482628
30	N_{10}-N_{11}-N_{12}	120.000000	471.482628
31	N_{11}-N_{12}-N_{15}	120.000000	151.692628

CONCLUSION

The present work indicates that the best conformation of 4-pyridylmethytetarzole was found to be -54811.7500 kcal/mol which is the minimum potential energy calculated by Argus Lab software. At this point 4-pyridylmethytetarzole will be more active to interact with the receptors. Such types of interactions are significant for drug- receptor interactions.

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