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A computational study on the 5-substituted 1H-tetrazoles: Structure, stability and aromaticity

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Abstract: The tetrazole moiety exhibits a wide and growing number of applications. This nitrogen-rich system is used in propellants, explosives and pharmaceuticals.A tetrazole molecule has prepared via [3+2] cycloaddition reaction starting from nitrile and sodium azide.The mechanism of tetrazole formation was studied theoretically by Barry Sharpless.In the present paper, the stabilization energy values of 5-substituted 1H-tetrazoles have been computed by the application of density functional theory (DFT) method by proper isodesmic reactions. Total energies, nucleus-independent chemical shift (NICS) and HOMO-LUMO gaps values have been calculated in order to determination of the stability, aromaticity and reactivity for the 5-substituted 1H-tetrazoles. And also, the geometrical parameters have been used for confirmation of observations.The isodesmic reactions revealed that tetrazoles containing electron-donating substituents have great stabilization energies, while the molecules containing electron-withdrawing substituents have low stabilization energies. It is deduced from the NICS data that the aromaticity of molecules decreases with increasing the interference of ring current. The HOMO-LUMO gaps calculation showed that 5-nitro-1H-tetrazole is more reactive than other tetrazole derivatives.

Keywords: Density functional theory, Tetrazoles, Stability, Aromaticity, Reactivity.

Introduction

Nitrogenis thelightestpnictogenand it is a colorless and odorlessdiatomicgas at room temperature [1]. Many industrially important materials, such asammonia,nitric acid, organicnitrates (propellantsandexplosives), andcyanides, contain nitrogen [2].It is notable for the range of explosively unstable compounds that it can produce [3]. Nitrogen triiodide (NI_3), Nitroglycerin and trinitrotoluene(TNT)are extremely sensitive contact explosives [4]. One main group of nitrogen compounds is related to the five-membered heterocyclic rings such as triazoles and tetrazoles.Tetrazolesare synthetic organic heterocyclic compounds, consisting of a five-member ring of fournitrogenand onecarbonatom.

There are several pharmaceutical agents which containtetrazole moieties, for instance tetrazole containing peptide inhibitors of renin[5]. In medicinal chemistry, the tetrazole ring can act as a metabolically stablebioisosterefor thecarboxylate group [6]. And also, this nitrogen-rich ring system is used in propellants and explosives [7-9].A tetrazole molecule has greater synthetic interest, prepared via [3+2] cycloaddition reaction starting from nitrile and sodium azide. Generally, a mixture of nitrile, sodium azide, and a proton source (to generate hydrazoic acid in situ) is heated in a suitablesolvent at relatively high temperature to produce, in most cases, good yields of tetrazoleproducts [10].The mechanism of tetrazole formation was studied theoretically by Barry Sharpless*et al.* in 2002 [11]. So far, many tetrazole compounds have been synthesized [12]. They are classified by the nature and substitution pattern of ring system [13]. In this paper, I studied theoretically the

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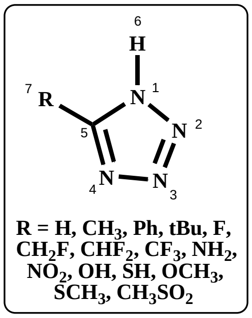
structure, stability and aromaticity of 5-substituted 1H-tetrazoles by density functional theory (DFT) calculations. The use of computational chemistry is in understanding a problem more completely [14].

Results and discussion

Stabilization energies:

According to Figure **1**, a group of tetrazoles substituted on position 5 are studied here.



R = H, CH_3, Ph, tBu, F, CH_2F, CHF_2, CF_3, NH_2, NO_2, OH, SH, OCH_3, SCH_3, CH_3SO_2

Figure 1: Structures of studied 5-substituted 1H-tetrazoles.

The tetrazole substituents (R) are H, Me, tBu, Ph, CF_3, CH_2F, CHF_2, NH_2, NO_2, OH, OMe, SH, SMe, F and $MeSO_2$.The stabilization energy (SE), which is on the basis of isodesmic reactions, is considered to be the most basic operational criterion in influencing the reactions and the physicochemical behavior [18]. There are some methods for calculation of stabilization energy (SE) from different isodesmic reactions [19]. An isodesmic reaction is the actual or hypothetical reaction in which the types of bonds that are made in forming the products are the same as those which are broken in the reactants [20]. Systems with negative SE are stabilized but systems with positive SE are destabilized [21].It should be used various isodesmic reactions to revolution of the SE correction of the studied molecules. Here, I use four isodesmic reactions (Figure **2**) for estimation of the stability of the 5-substituted 1H-tetrazoles. The isodesmic reactions (Eqs. 1-4) are based on cyclic olefinic and conjugated analogues. The stabilization energy (SE) for all molecules was obtained at the B3LYP/6-31G(d) level of theory. The SE values are listed in Table **1**. The dependence between studied isodesmic reactions is showed for all molecules (Figure **3**). Correlation coefficients (R^2=1) for these four equations present a high convergence. As can be seen from the data, the SE order of 5-substituted 1H-tetrazoles (R=various groups) is: Ph>tBu>Me>MeS> NH_2> H >MeO> OH > SH > CH_2F > CHF_2> CF_3> $MeSO_2$> F > NO_2.

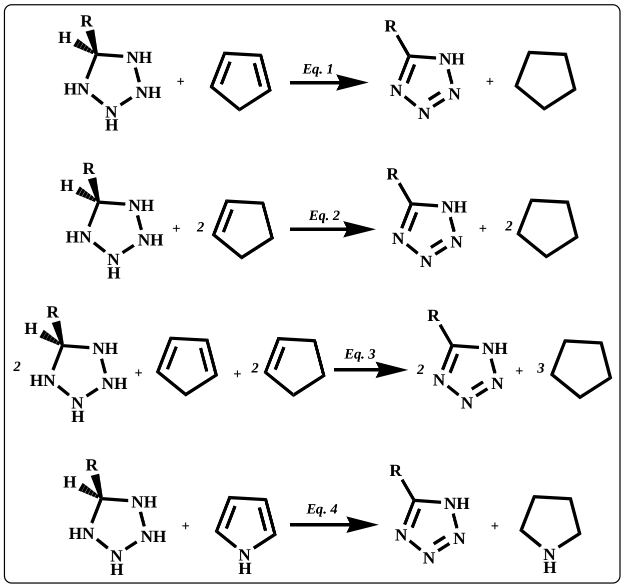


Figure 2: All different isodesmic formal equations for the calculation of the stabilization energies (SE) of the 5-substituted 1H-tetrazoles.

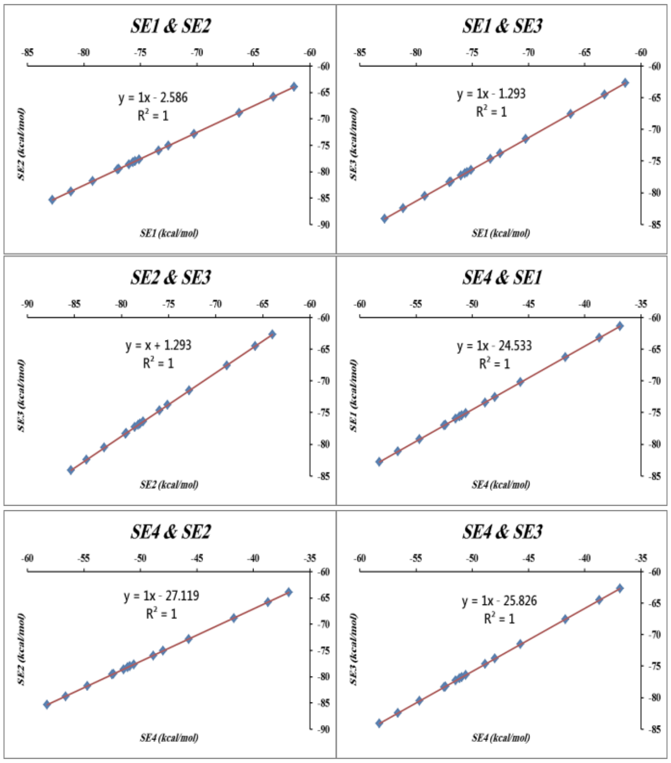


Figure 3: The dependence between aromatic stabilization energies for the 5-substituted 1H-tetrazoles.

The results of the isodesmic reactions show all molecules are stable. The molecules containing electron-donating substituents on position 5 are more stable than the molecules containing electron-withdrawing substituents on position 5.

Table 1: Estimated stabilization energies (SE) for all molecules calculated using different isodesmic reactions at B3LYP/6-31G(d) level of theory.

R	Stabilization Energy (kcal/mol) B3LYP/6-31G(d)			
	Eq. 1	Eq. 2	Eq. 3	Eq. 4
H	-76.007	-78.593	-77.300	-51.473
NH_2	-76.901	-79.487	-78.194	-52.367
Me	-79.238	-81.824	-80.531	-54.704
Ph	-82.807	-85.393	-84.100	-58.274
tBu	-81.154	-83.740	-82.447	-56.620
SH	-75.104	-77.690	-76.397	-50.570
MeS	-77.021	-79.607	-78.314	-52.487
OH	-75.448	-78.034	-76.741	-50.914
MeO	-75.644	-78.230	-76.937	-51.110
CH_2F	-73.389	-75.975	-74.682	-48.855
CHF_2	-72.524	-75.110	-73.817	-47.991
CF_3	-70.233	-72.819	-71.526	-45.700
$MeSO_2$	-66.247	-68.833	-67.540	-41.713
F	-63.220	-65.806	-64.513	-38.687
NO_2	-61.398	-63.984	-62.691	-36.864

Table 2: Computed bond lengths for all molecules at B3LYP/6-31G(d) level of theory.

R	N1-N2	N2-N3	N3-N4	N4-C5	N1-C5	N1-H6	C5-R
H	1.353	1.292	1.366	1.316	1.347	1.011	1.080
NH_2	1.348	1.297	1.362	1.320	1.351	1.011	1.406
Me	1.355	1.291	1.364	1.320	1.353	1.011	1.491
Ph	1.353	1.293	1.357	1.327	1.354	1.010	1.464
tBu	1.354	1.291	1.364	1.321	1.354	1.010	1.511
SH	1.360	1.288	1.364	1.321	1.350	1.011	1.757

MeS	1.360	1.288	1.366	1.323	1.352	1.011	1.752
OH	1.366	1.288	1.368	1.314	1.344	1.010	1.334
MeO	1.364	1.288	1.369	1.317	1.349	1.010	1.327
CH_2F	1.357	1.289	1.366	1.317	1.352	1.011	1.501
CHF_2	1.349	1.294	1.363	1.316	1.347	1.012	1.495
CF_3	1.347	1.296	1.361	1.314	1.347	1.012	1.502
$MeSO_2$	1.346	1.297	1.364	1.314	1.346	1.013	1.799
F	1.360	1.292	1.368	1.303	1.345	1.011	1.313
NO_2	1.341	1.303	1.358	1.310	1.344	1.013	1.451

Bond length unit: Aº

The geometry of tetrazole molecules containing Ph, tBu, Me, MeS and NH_2 substituents is more similar to geometry of 1H-tetrazole (Tables **2** and **3**).

In contrast, for molecules (R=MeO, OH) the SE value is lower than SE value of 1H-tetrazole. These molecules have more oxygen balance, and because of this reason, their stability is lower than 1H-tetrazole. From the Tables **2** and **3**, it is observed that the S-C bond is polarized in 1H-tetrazole-5-thiol and 5-(methylsulfonyl)-1H-tetrazole. The polarization of S-C bond is the reason of instability of them. High electron repulsion of nitrogen atoms due to small bonds between atoms is cause of the instability of 5-fluoro-1H-tetrazole.The lowest SE is corresponded to 5-nitro-1H-tetrazole due to having more oxygen balance.

Table 3: Computed bond angles for all molecules at B3LYP/6-31G(d) level of theory.

R	N1-N2-N3	N2-N3-N4	N3-N4-C5	N4-C5-N1	N2-N1-C5	N4-C5-R	H6-N1-C5-R
H	105.871	111.389	105.676	108.446	108.618	126.714	0.091
NH_2	105.696	111.327	106.060	107.722	109.196	130.401	0.009
Me	105.670	111.343	106.404	107.348	109.236	126.699	0.020
Ph	105.738	111.340	106.659	106.938	109.325	126.229	0.015
tBu	105.674	111.242	106.641	107.025	109.419	127.479	-0.023
SH	105.802	111.743	105.660	108.272	108.523	127.395	-0.035
MeS	105.841	111.683	105.805	107.983	108.688	127.852	0.054
OH	105.878	111.755	105.172	109.358	107.837	128.191	-0.213
MeO	105.906	111.823	105.206	109.066	108.000	129.256	-0.131
CH_2F	105.777	111.546	105.915	108.067	108.696	127.292	0.003
CHF_2	106.064	111.187	105.769	108.418	108.562	126.647	4.311
CF_3	106.046	111.302	105.540	108.704	108.408	127.285	0.724

$MeSO_2$	106.208	111.175	105.343	109.017	108.256	128.540	-2.941
F	105.909	111.859	104.535	110.444	107.254	127.108	0.015
NO_2	106.230	111.344	104.816	109.886	107.723	128.194	0.002

Bond angle unit: degree

NICS study of the 5-substituted 1H-tetrazoles:

The aromatic ring current is an effect observed inaromaticmolecules such asbenzeneandnaphthalene. If amagnetic field is directedperpendicular to the plane of the aromatic system, a ring current is induced in the delocalizedπ electrons of the aromatic ring. This is a direct consequence ofAmpere's law; since the electrons involved are free to circulate, rather than being localized in bonds as they would be inthe most non-aromatic molecules, they respond much more strongly to the magnetic field [22].NICS is acomputational method that calculates the absolutemagnetic shieldings at the center of the ring taken with reversed sign. In this method negative NICS values indicate aromaticity and positive values antiaromaticity [23].The NICSvalues for all molecules were obtained at the B3LYP/6-31G(d) level of theory. The NICS values are listed in Table **4**. It is observed that all the molecules are aromatic. The data of the Table **4** indicate that the NICS order of 5-substituted 1H-tetrazoles (R=various groups) is: H > CF_3> CHF_2> $MeSO_2$> CH_2F > CH_3> SH >tBu>MeS> NO_2> NH_2> F >Ph>MeO> OH. It is deduced that all the substituents reduce the aromaticity character of tetrazole ring due to interference in the ring current. The resonance effect of substituents is more than the induced effect (electron-donating groups > electron-withdrawing groups) of substituents in the interference of the tetrazole ring current. From these observations, Ifound that the aromaticity of molecules decreases with increasing the interference of ring current.The comparison between the SE and NICS orders shows that the NICS index can't be used to explain the stability of compounds because the stability of tetrazole molecules are considered by two parameters: a) aromaticity (resonance of non-saturated bonds) of rings and b) the electrostatic repulsion effect of non-bonded electrons of nitrogen atoms in the tetrazole rings. Then, the nucleus independent chemical shift index explain only the aromaticity character of the studied compounds and it can't explain the stability of the molecules.

Table 4: Calculated NICS(0) for all molecules at B3LYP/6-31G(d,p) level of theory.

R	NICS(0)
H	-14.0614
NH_2	-11.4697
Me	-12.5375
Ph	-11.0857
tBu	-12.3448
SH	-12.4820
MeS	-11.9896
OH	-10.7928
MeO	-10.9809
CH_2F	-12.8678

CHF_2	-13.0480
CF_3	-13.2609
$MeSO_2$	-13.0341
F	-11.1789
NO_2	-11.6025

Frontier orbitals energies:

Fukui realized that a good approximation for reactivity could be found by looking at the frontier orbitals (HOMO/LUMO) [24]. Frontier molecular orbital (FMO) theory simplifies reactivity to interactions between the HOMO and the LUMO orbitals [25].The HOMO-LUMO gaps could explain the kinetic stability and reactivity of species [26]. We know that the reactivity of molecules increases with decreasing the kinetic stability of molecules.The values of H-L gaps are listed in Table **5**.

Table 5: Calculated HOMO-LUMO gaps (eV) for all molecules at B3LYP/6-31G(d) level of theory**.**

R	B3LYP/6-31G(d)		
	HOMO (a.u.)	LUMO (a.u.)	Gap_{L-H} (eV)
H	-0.29310	-0.02324	7.3433
NH_2	-0.27501	-0.01486	7.0791
Me	-0.28412	-0.01635	7.2865
Ph	-0.25466	-0.05621	5.4001
tBu	-0.28026	-0.01231	7.2913
SH	-0.26889	-0.02354	6.6764
MeS	-0.25199	-0.01733	6.3855
OH	-0.28096	-0.01298	7.2922
MeO	-0.27088	-0.00855	7.1384
CH_2F	-0.29330	-0.02760	7.2301
CHF_2	-0.30667	-0.04485	7.1245
CF_3	-0.31246	-0.05067	7.1237
$MeSO_2$	-0.31465	-0.05911	6.9537
F	-0.30500	-0.03067	7.4650
NO_2	-0.32552	-0.13449	5.1982

The results show that the reactivity order of 5-substituted 1H-tetrazoles (R=various groups) is: NO_2>Ph>MeS> SH > $MeSO_2$> NH_2> CF_3> CHF_2>MeO> CH_2F >Me>tBu> OH > H > F. The higher oxygen balance (-6.96%) of 5-nitro-1H-tetrazole causes this molecule becomes unstable and highly reactive.

Conclusion

The relative energies, isodesmic reactions, geometrical parameters, NICS and frontier orbitals energies calculations were applied to determine the stability, aromaticity and reactivity of 5-substituted 1H-tetrazoles (substituents= H, Me, tBu, Ph, CF_3, CH_2F, CHF_2, NH_2, NO_2, OH, OMe, SH, SMe, F and $MeSO_2$) at B3LYP/6-31G(d) level of theory. The isodesmic reactions revealed that tetrazoles containing electron-donating substituents have great stabilization energies, while the molecules containing electron-withdrawing substituents have low stabilization energies. It is deduced from the NICS data that the aromaticity of molecules decreases with increasing the interference of ring current. The HOMO-LUMO gaps calculation showed that 5-nitro-1H-tetrazole is more reactive than other tetrazole derivatives. The computed geometrical parameters confirmed our observations.

Computational method:

All theoretical studies were carried out with the Gaussian 03 computational package [15].The computational method employed for the tetrazole derivatives calculations was the B3LYP/6-31G(d) level of theory. The term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3)local correlation functional [16] and Lee, Yang, Parr (LYP) correlation correctionfunctional [17].The geometry of structures was optimized without any structural orsymmetry restrictions in the gas phase.

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