Computational Study of C-Substituted Tetrazole Tautomers: Magnetic and Structural Based Degree of Aromaticity

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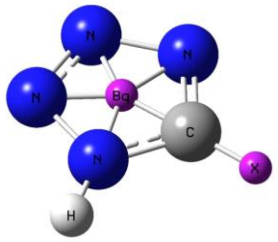
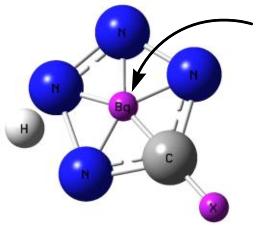
Abstract: ***This study focused on the influence of substitution on the degree of aromaticity of tetrazole tautomers. All the structures were fully optimised at the DFT B3lyp (three parameter hybrid functional of Becke using Lee-Yang-Parr correlation function) method incorporating various basis sets. Interesting results were obtained regarding aromatic properties for the 1H- and 2H-Tetrazole isomers substituted with the selected substituent's. Magnetic and Geometry based degree of aromaticity show strong aromatic character.***

Keywords: Tetrazole, Aromaticity, DFT, NICS, Bird index.



1H-Tetrazole



Ghost atom-Banqua
Point of measuring
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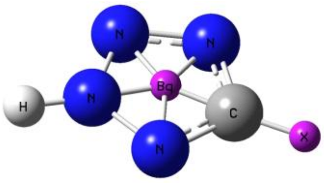
Transition State structure



2H-Tetrazole

X= NH_2-,OH-, CH_3-,C_2H_5-,NO_2-,COOH-, C_6H_5-

1. Introduction

Tetrazoles are well known heterocyclic compounds in organic chemistry, which draw a lot of attention for many reasons. Biological and medicinal applications are the major issues, which make the compound valuable and an outstanding among the heterocycles. High energetic properties of tetrazole recently draw attentions from chemists in the field of experimental and theoretical studies. The presence of several reaction sites and the possibility of prototropy in tetrazole afford the conditions for their use in organic and bio-organic synthesis as reagents and catalysts. The amount of publications devoted to the molecular structure, synthetic methods, chemical and physicochemical properties of tetrazole constantly increases. These compounds have specific thermo chemical properties and exhibit multiple reactivity. Moreover, being highly energetic nitrogen rich compounds, explosives materials, rocket fuel and gas generating compositions were developed from a number of tetrazole derivative[1,2,3]. The tetrazole ring is the fragment of a number of modern drugs such as antibacterial, anti–allergic, anti–inflammatory, angiotensine II antagonists[4]. The numerous possibilities of coordination of tetrazole ring with metal ions permit to use these compounds as effective complexones and as corrosion inhibitors[5]. The degree of aromaticity of the ring systems between the two tautomers were examined using simple parameters; NICS and Bird Index.

2. Computational Details

All the Quantum-chemical calculations in this work were performed using Gaussian03 program. Since the aromaticity parameters are highly sensitive to the molecular geometry, all the structures are fully optimized at the Density Functional Theory of B3LYP (three–parameter hybrid functional of Becke using Lee-Yang-Parr correlation functional) method using the standard 6-31G, 6-31+G*, 6-31**G++ and cc-pVTZ basis sets to obtain a comparable results as well as to ensure reliable geometry prediction. Single point frequency calculations were performed at the selected basis sets to identify the transition state geometries. Diffuse functions have long been known to be extremely important in the description of systems having lone pair of electrons such as nitrogen atom. Also, many previous theoretical studies show that theoretical calculation performed at the B3lyp methods are as good high level ab initio results. In order to examine the efficiency of our choice of basis sets in terms of consistency and reliability, calculated degrees of aromaticity were carefully tabulated for each of the isomers. The purpose of this work is to provide reliable computational data for tetrazole in relation to its aromatic properties by investigating substituted and unsubstituted isomers for both the tautomers.

3. Results and discussions

Nucleus Independent Chemical shift (NICS) index of Aromaticity

Magnetic indices of aromaticity are completely based on the π-electron ring current that is induced when the system is exposed to an external magnetic field[6]. Among the indices, the NICS proposed by Schleyer and co-worker is the most widely used. The NICS is defined as the negative value of the absolute shielding computed at the ring centre or at some other interesting point of the system[7]. The magnetism based index NICS is simply a negative value of the absolute shielding estimated at the centre of the ring (NICS) and 1 Å above plane of the ring[8]. Rings with large negative NICS values are considered aromatic. The more negative the NICS values, the more aromatic the rings are. NICS mainly concerned with the particular magnetic properties of the aromatic ring, and is sensitive to the σ–electronic effect and depends on the ring size and the level of theory applied. Aromatic systems exhibit diatropic π–ring current while antiaromatic ring possess a paratropic one. It is the presence of a true ring current that is used to establish whether a molecule is aromatic or not[9]. The NICS follows the chemical shift sign convention (negative upfield), which is opposite to the shielding (positive upfield). Exocyclic protons exhibit characteristic low-field (diatropic) chemical shift due to the induction of a diamagnetic ring current in a cyclic π–system[10]. The NICS values are well defined and easy to calculate, and recently, it was observed that the NICS values are influence by factors arising from the σ framework of the ring[11]. The NICS index is more closely related to the uniformity of distribution of π-electron density around the ring rather than the equalization of bond lengths, i.e. the NICS values are more dependent on π–electron distribution rather than the geometry of the ring systems. This equates to the delocalization of the lone pair and an uniform distribution of the π-electron density on the atoms of five-membered ring for optimum aromaticity. Therefore, ring nitrogen facilitates optimal redistribution of π-electron density around the ring[12]. In this study, we strongly suspect the difference in electronegativity and size of the substituents in the ring to cause polarization of the σ–skeleton and the π-system, therefore considerable changes in the degree of aromaticity could be observed. We have computed NICS values at the centre of the ring [NICS$_{(0)}$] and also at 1Å above plane of the ring at the B3LYP/6-31G, B3LYP/6-31+G*, B3LYP/6-311++G** and B3LYP/cc-pVTZ levels of theory. The results were shown at the following Tables.

Table 1. NICS$_{(0)}$ index at the B3LYP/6-31G and B3LYP/6-31+G* levels of theory.

Compounds	NICS$_{(0)}$ (ppm)					
	B3LYP/6-31G			B3LYP/6-31+G*		
	1H-Tz	2H-Tz	Ts	1H-Tz	2H-Tz	Ts
Tetrazole	-12.06	-12.27	-12.97	-13.97	-14.19	-13.28
Aminotetrazole	-10.34	-11.19	-12.08	-11.14	-11.95	-10.26
Hydroxytetrazole	-9.30	-11.58	-10.97	-10.71	-12.60	-9.91
Methyltetrazole	-10.83	-11.53	-11.72	-12.48	-13.01	-11.70
Ethyltetrazole	-10.77	-11.79	-12.04	-12.17	-13.29	-11.83
Nitrotetrazole	-9.10	-11.79	-10.21	-11.58	-13.66	-10.96
Carboxytetrazole	-10.52	-11.47	-11.49	-12.69	-13.83	-11.86
Phenyltetrazole	-9.73	-10.59	-10.96	-10.91	-11.70	-10.93

Table 2: NICS$_{(0)}$ index at the B3LYP/6-311++G** and B3LYP/cc-pVTZ levels of theory.

Compounds	NICS$_{(0)}$ (ppm)					
	B3LYP/6-311++G**			B3LYP/cc-pVTZ		
	1H-Tz	2H-Tz	Ts	2H-Tz	1H-Tz	Ts
Tetrazole	-14.39	-14.63	-13.86	-14.20	-14.41	-13.42
Aminotetrazole	-11.45	-12.13	-10.56	-11.53	-11.99	-10.57
Hydroxytetrazole	-11.09	-12.85	-10.58	-10.81	-12.78	-10.33
Methyltetrazole	-12.62	-13.25	-12.28	-12.44	-13.15	-11.74
Ethyltetrazole	-12.47	-13.87	-12.32	-12.26	-13.74	-12.15
Nitrotetrazole	-12.13	-13.87	-11.89	-11.85	-13.84	-11.34
Carboxytetrazole	-13.02	-13.85	-12.35	-12.73	-13.85	-12.16
Phenyltetrazole	-11.18	-11.77	-10.50	-10.86	-11.72	-9.99

Table 3: NICS$_{(1)}$ index at the B3LYP/6-31G and B3LYP/6-31+G* levels of theory.

Compounds	NICS$_{(1)}$ (ppm)					
	B3LYP/6-31G			B3LYP/6-31+G*		
	1H-Tz	2H-Tz	Ts	1H-Tz	2H-Tz	Ts
Tetrazole	-12.74	-13.67	-15.20	-13.97	-13.69	-15.39
Aminotetrazole	-10.63	-11.87	-12.26	-10.85	-11.35	-12.26
Hydroxytetrazole	-10.69	-12.23	-12.49	-10.71	-11.85	-12.48
Methyltetrazole	-12.19	-13.20	-14.39	-12.69	-12.94	-14.68
Ethyltetrazole	-12.25	-12.45	-14.34	-12.22	-12.84	-15.39
Nitrotetrazole	-11.31	-12.63	-13.42	-12.30	-12.89	-13.92
Carboxytetrazole	-12.65	-13.34	-14.42	-13.21	-13.58	-14.69
Phenyltetrazole	-11.75	-12.34	-13.36	-11.35	-12.09	-13.36

Table 4: $NICS_{(1)}$ index at the B3LYP/6-311++G** and B3LYP/cc-pVTZ levels of theory

Compounds	$NICS_{(1)}$ (ppm)					
	B3LYP/6-311++G**			B3LYP/cc-pVTZ		
	1H-Tz	2H-Tz	Ts	1H-Tz	2H-Tz	Ts
Tetrazole	-13.32	-13.86	-15.61	-13.30	-13.85	-14.93
Aminotetrazole	-10.77	-11.41	-12.52	-10.59	-11.48	-11.49
Hydroxytetrazole	-10.75	-11.92	-12.67	-10.59	-11.91	-11.73
Methyltetrazole	-12.29	-13.25	-14.73	-12.44	-13.49	-13.89
Ethyltetrazole	-12.49	-13.88	-14.66	-12.60	-13.99	-13.97
Nitrotetrazole	-12.54	-13.12	-14.29	-12.39	-13.15	-13.32
Carboxytetrazole	-13.02	-13.76	-14.98	-13.22	-13.73	-14.14
Phenyltetrazole	-11.46	-12.32	-13.37	-11.44	-12.10	-12.44

Shielding in ppm at $NICS_{(0)}$ has been characterized by small deviation for substituted isomers when compared to unsubstituted tetrazole. B3lyp/6-31G level predict the unsubstituted transition state as having the highest π-electron distribution (-12.97) around the heterocyclic ring. Except for hydroxy and nitro substituted isomers, all the isomers predicts the transition state species to be more aromatic over the 1H- and 2H-tautomers. This unexpected result suggest that the B3lyp/6-31G level is not suitable for the study of our titled compounds in relation to its magnetic property of aromaticity.

Prediction of aromaticity has similar results for the other three theoretical levels where the 2H-isomers was computed to have the highest NICS values for each and every isomer. But the magnetic properties are not influence much as expected by the substituents. The unsubstituted tetrazole predicts $NICS_{(0)}$ values around -13.28 to -14.63, which in fact, is higher than benzene $NICS_{(0)}$ values (-11.5)[6]. Our computation at the B3LYP/6-31G, B3LYP/6-31+G*, B3LYP/6-311++G** and B3LYP/cc-pVTZ levels of theory predicts the $NICS_{(0)}$ values for all the 1H- and 2H-tautomers as higher than benzene except for the hydroxy and phenyl-substituted 1H-tautomers. Except for the hydroxy and ethyl substituted tetrazole, calculations of $NICS_{(1)}$ predicts higher aromaticity over the corresponding tautomers for all the isomers at all the applied theoretical levels. The $NICS_{(1)}$ values for unsubstituted tetrazole are normally predicted to be around -14.12 to -14.64 at 1Å above the plane[11]. $NICS_{(1)}$ values from our calculation reveals unexpectedly low values, where only some transition state species have $NICS_{(1)}$ values ~ -14.0 and above. Therefore, from our point of view, computation of NICS values at 1Å above plane of the ring is not appropriate as compare to plane of the ring for the study of magnetic aromaticity index for tetrazole and its substituted isomers.

Bird (I_5) Index of Aromaticity

This index is completely based on geometry and was calculated by the following relations[10,13,14,15]:

$\boldsymbol{I_5} = 100 - (V/35)\ 100$, Where, '**V**' is the degree of uniformity of the bond order

$\mathbf{V} = 100/N \sqrt{\sum (N-\overline{N})^2/n}$, '**N**' is the bond order, $\mathbf{N} = (a/l^2) - b$

$\overline{\mathbf{N}}$ is the arithmetic mean of the bond order, '**n**' is the number of bond

'**a**' and '**b**' are empirical constants: **a** = 6.48 for C-N bond, 5.28 for N-N bond

b = 2.00 for C-N bond, 1.41 for N-N bond

Table 5: The I_5 (Bird) index at the B3LYP/6-31G, B3LYP/6-31+G*, B3LYP/6-311++G**.

Compounds	B3LYP/6-31G			B3LYP/6-31+G*		
	1H-Tz	2H-Tz	Ts	1H-Tz	2H-Tz	Ts
Tetrazole	68.19	86.41	34.74	75.77	90.10	62.73
Aminotetrazole	66.69	84.89	16.49	73.48	88.07	53.35
Hydroxytetrazole	66.38	86.71	28.10	72.29	89.47	53.02
Methyltetrazole	69.04	84.38	41.18	76.56	88.78	62.46
Ethyltetrazole	69.92	85.27	41.59	87.59	88.51	62.27
Nitrotetrazole	72.95	42.15	57.44	79.75	89.70	67.80
Carboxytetrazole	77.78	83.71	57.66	68.02	87.62	68.86
Phenyltetrazole	74.54	84.73	42.79	79.50	87.29	63.02

Table 6: The I_5 (Bird) index at the B3LYP/6-311++G** and B3LYP/cc-pVTZ levels of theory.

Compounds	B3LYP/6-311++G**			B3LYP/cc-pVTZ		
	1H-Tz	2H-Tz	Ts	1H-Tz	2H-Tz	Ts
Tetrazole	74.72	91.79	61.89	74.46	89.51	59.61
Aminotetrazole	71.06	86.86	51.44	70.95	86.25	44.56
Hydroxytetrazole	70.96	88.79	56.89	72.28	88.74	53.96
Methyltetrazole	74.67	87.47	61.59	74.53	87.84	60.18
Ethyltetrazole	60.92	87.49	41.17	74.25	53.36	58.92
Nitrotetrazole	79.60	88.14	66.28	77.72	90.49	64.53
Carboxytetrazole	81.17	86.98	68.26	74.46	87.06	66.14
Phenyltetrazole	77.43	86.39	79.17	78.06	86.67	60.29

.The overall calculations from I_5 predict high aromatic properties as compare to fully aromatic benzene, whose aromaticity is assumed as equal to 100 [16,17,18]. But, the B3lyp/6-31G theory predict 16.49 and 28.10 for the transition state of C-substituted amino- and Hydroxy-tetrazole. Also, the 2H-isomers are surprisingly found to be less aromatic than 1H-isomer in the case of nitro substituted isomers from the B3lyp/6-31G level and ethyl substituted isomers from the B3lyp/cc-pVTZ level.

4. Conclusions

1. The influence of substituents on magnetic properties of tetrazole is low. Our calculations of NICS values reveal substitution does not facilitate π-electron delocalization within the ring system to any appreciable extent. It is also interesting to note that the distribution of π-electron density is higher at the centre of the ring than above plane of the ring.
2. From our calculation of geometry based index of aromaticity (Bird index), the 2H-tautomer generally predict higher degree of aromatic character over 1H-tautomer except for few cases and these results also support stability of 2H-tautomer over 1H-tautomer since lack of aromaticity results in less favored tautomer, and thus, lower stability. Substitution with electronegative species results in lowering of aromatic properties.
3. Based on the NICS and Bird indices, our calculations point out that tetrazole tautomers predict high degree of aromaticity for all the substituted isomers. Therefore, we concluded that the tetrazole system is a strong cyclic π-

system, which rendered remarkable resistance against electron withdrawing and electron donating species.

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