Earthline Journal of Chemical Sciences
E-ISSN: 2581-9003; CODEN: EJCSB4
Volume 10, Number 2, 2023, Pages 213-227
https://doi.org/10.34198/ejcs.10223.213227

DFT Treatment of Betazole Tautomerism

Lemi Türker

Department of Chemistry, Middle East Technical University, Üniversiteler, Eskişehir Yolu No: 1, 06800 Çankaya/Ankara, Turkey; e-mail: lturker@gmail.com; lturker@metu.edu.tr

Abstract

Betazole belongs to pyrazole type medicines and selectively targets and binds to the H2-type receptors. Tautomerism can only be demonstrated in pyrazole derivatives and not in the pyrazole itself. In the present density functional treatment of tautomers of betazole (within the constraints of density functional theory) calculations have been performed at the level of B3LYP/6-311++G(d,p). Betazole may exhibit 1,3- and 1,5-type proton tautomerism involving pyrazole ring system so that in some tautomers aromaticity of the ring is destroyed. The results have revealed that all the tautomers possess thermo chemically favorable formation values at the standard conditions and are electronically stable. Some quantum chemical and spectral properties of those tautomeric systems as well as nucleus independent chemical shift (NICS) values for the aromatic ones have been obtained and discussed.

1. Introduction

Betazole (also known as ametazole) [1-4] is a histamine H2 receptor agonist with diagnostic application. Betazole hydrochloride is known as gastramine. Betazole is used as a stimulant [5]. in preference to histamine because of its specificity for the H_2 receptor and its advantage of not generating the undesirable side effects that histamine would induce. It therefore does not require concomitant use of antihistaminic compounds to block the actions of histamine at other histamine receptor types.

Betazole selectively targets and binds to the H2 receptor, thereby mimicking the effect of histamine on these receptors. This may lead to an increase in gastric secretions. Betazole can be used in gastric function tests. The test can be used in diagnosis of

Received: June 21, 2023; Accepted: July 27, 2023; Published: July 30, 2023

Keywords and phrases: betazole; ametazole; tautomerism; DFT calculations; NICS.

diseases such as Zollinger-Ellison syndrome where there is excess acid production, in this case driven by over production of gastrin. This procedure can lead to complications and should be avoided in subjects with coronary artery disease [6]. It is also used in diagnosis of gastritis in association with a test for secretin activity. It is used to test the effectiveness of H_2 receptor blocking drugs such as nizatidine [7].

A new synthesis of betazole was described by Jones and Mann [8,9] and also enzymatic formation of it was reported [10]. In the literature ample number of articles exist about the medicinal aspects of betazole [11-17].

Betazole belongs to pyrazole family of medicines. Note that the important physical property of pyrazole is the existence of tautomerism, which can only be demonstrated in pyrazole derivatives and not in the pyrazole itself. If pyrazole is tautomeric, then the positions 3 and 5 will be identical; if pyrazole is not tautomeric, then these positions are different [2,19]. Some molecular orbital calculations were performed on betazole and similar compounds [19-21].

2. Method of Calculations

In the present study, all the initial structure optimizations of the closed-shell structures leading to energy minima have been achieved by using MM2 method then followed by semi empirical PM3 self consistent fields molecular orbital (SCF MO) method [22-24]. Afterwards, the structure optimizations have been managed within the framework of Hartree-Fock (HF) and finally by using density functional theory (DFT) at the level of B3LYP/6-311++G(d,p) [25,26]. It is worth mentioning that the exchange term of B3LYP consists of hybrid Hartree-Fock and local spin density (LSD) exchange functions with Becke's gradient correlation to LSD exchange [27]. The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [28] and Lee, Yang, Parr (LYP) correlation correction functional [29]. In the present study, the normal mode analysis for each structure yielded no imaginary frequencies for the $3N–6$ vibrational degrees of freedom, where N is the number of atoms in the system. This search has indicated that the structure of each molecule considered corresponds to at least a local minimum on the potential energy surface. Furthermore, all the bond lengths have been thoroughly searched in order to find out whether any bond cleavage occurred or not during the geometry optimization process. All these computations were performed by using SPARTAN 06 [30]. Whereas the nucleus-independent chemical shift, NICS(0), calculations have been performed by using Gaussian 03 program [31].

3. Results and Discussion

Since tautomers having different structures possess dual reactivity, it is anticipated that betazole may exhibit 1,3- and 1,5-proton tautomerism and should display variable biological properties (beside others) depending on its tautomer content (allelotropic mixture [32,33]). Note that substances which are isomeric under certain conditions are tautomeric under more drastic conditions [32,33]. In the absence of any degenerate tautomeric process, the opportunity of observing two tautomeric forms, A and B arises [18]. However, in the literature structure of betazole seems not to be firmly established yet. In some articles or data bases, structure-B1 [1,4,19,34,35], whereas in the others structure-B2 [3,10,36] was considered for the tautomers (See Figure 1). Figure 1 shows 1,3- and 1,5-proton tautomerisms in betazole which is a 3-substituted pyrazole (For betazole, R: $CH_2CH_2NH_2$).

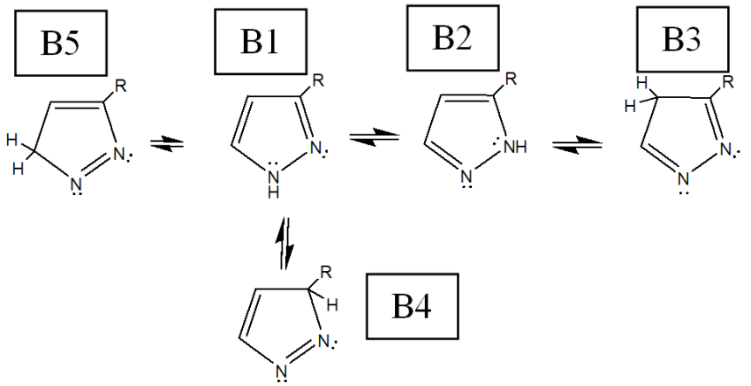


Figure 1. 1,3- and 1,5-Proton tautomerisms in 3-substituted pyrazoles (For betazole, R: $CH_2CH_2NH_2$).

Figure 2 shows the optimized structures of the betazole tautomers considered. The direction of the dipole moment vectors is shown as well. The dashed-lines indicate possible hydrogen bondings. Note that in tautomers B1 and B2 there exist 6π-electrons in cyclic conjugation. So, they are inner aromatics in which lone pair of one of the nitrogen atoms is included in the aromatic sextet. Tautomers B3-B5 do not have any cyclic conjugation in the ring.

In Figure 2, a noticeable point is that the directions of the dipole moment vectors in tautomers B1 and B2 are almost opposite to each other. Note that in B2 there is a possibility of hydrogen bonding formation which may lead to zwitter ion formation. The electronegativity of nitrogen atom at position-2 of B1 and B2 should be quite different.

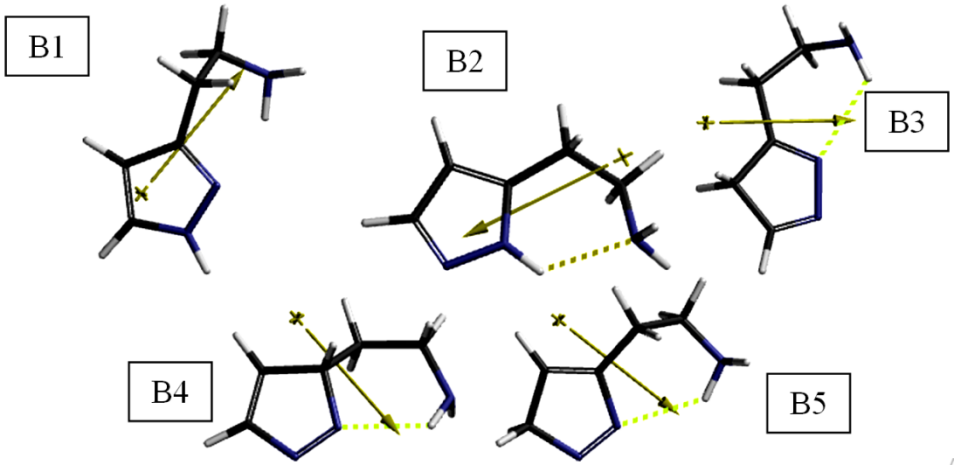


Figure 2. Optimized structures of the tautomers considered.

Table 1 lists some properties of the tautomers considered. There, the polarizability is defined according to the multivariable formula [30].

$$\text{Polarizability} = 0.08*V - 13.0353*h + 0.979920*h2 + 41.3791$$

where V and h are the Van der Waals volume and hardness, respectively. Hardness is defined as,

$$\text{Hardness} = -(\varepsilon_{HOMO} - \varepsilon_{LUMO})/2$$

where ε_{HOMO} and ε_{LUMO} are the molecular orbital energies of the highest occupied (HOMO) and the lowest unoccupied (LUMO) molecular orbital energies.

Note that tautomer-B2 has the lowest logP value and hydrophilic drugs (having low octanol/water partition coefficients) are found primarily in aqueous regions. Considering this fact together with its high dipole moment value, structure of tautomer-B2 should be more polar than B1.

The order of dipole moments is B1<B5<B4<B2<B3. Note that the amino group in B2 acts as an acceptor whereas in B4 and B5 it is a donor in hydrogen bonding process. Thus, dipole moments in B3-B5 are quite different from the one in tautomer-B2. Also the dipole moment values among B3-B5 differ from each other although the donor and acceptor sites are the same in those cases. The reason for that should be the electronegativity difference of nitrogen atom at position-2 of the ring for tautomers from B3 to B5.

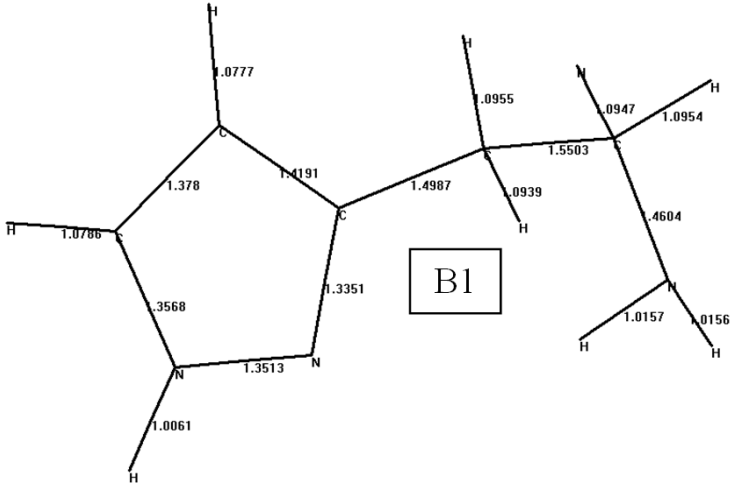
Polar surface areas (PSA) of the tautomers is defined as the amount of molecular surface area arising from polar atoms (N,O) together with their attached hydrogen atoms. Molecules with PSA values greater than 140 Å² tend to be poor at permeating cell membranes whereas to penetrate the blood-brain barrier a PSA value of a molecule should be less than 90 Å² [37,38]. Therefore, all the tautomers of present interest seem to have quite good penetrating ability the blood-brain barrier having the order of ease of B4>B3>B5>B2>B1.

Table 1. Some properties of the tautomers considered.

	Area (Å)	Volume	Ovality	Log P	Polarizability	PSA (Å²)	Dipole moment
B1	147.73	120.93	1.25	0.02	49.77	50.113	2.86
B2	145.20	120.55	1.23	-1.30	49.78	46.918	4.70
B3	145.55	120.76	1.23	-0.26	50.03	44.352	5.63
B4	144.60	120.73	1.22	0.67	50.16	44.070	4.33
B5	145.58	120.69	1.23	-0.02	50.13	45.126	4.09

Dipole moments in debye units. Polarizabilities in 10^{-30} m^3 units.

Figure 3 shows bond lengths of tautomers B1 and B2. As seen in the figure depending on the tautomerism, bond lengths of the pyrazole ring exhibit some variations which should affect the NICS values mentioned below.



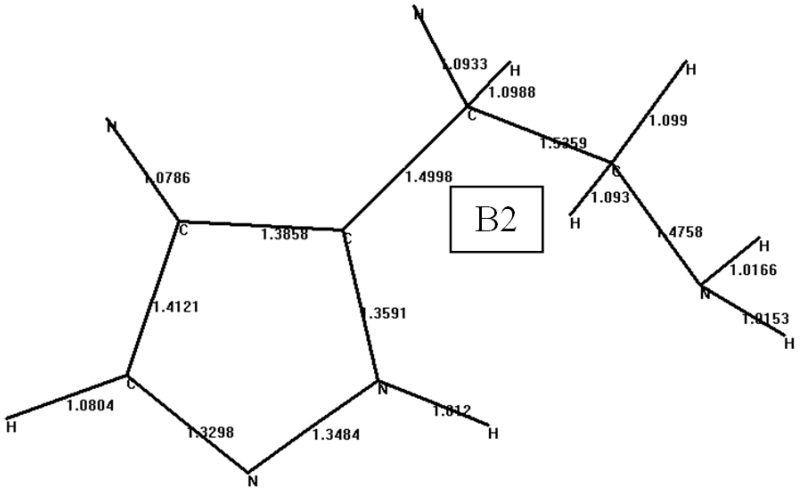


Figure 3. Bond lengths of tautomers B1 and B2.

Figure 4 displays the electrostatic potential maps of the tautomers considered. In the figure the red and blue colors stand for negative and positive potential regions, respectively. The most negative potential region in each tautomer coincides with the nitrogen atoms of the pyrazole ring and the amino group of the substituent.

Table 2 shows some thermo chemical values of the tautomers considered. As seen in the table all the tautomers possess exothermic heat of formation and favorable Gibb's energy of formation values at the standard states. The orders of H^o and G^o values (algebraically) are the same as B2<B1<B3<B5<B4, so that B2 is more exothermic and more favorable as compared to B1.

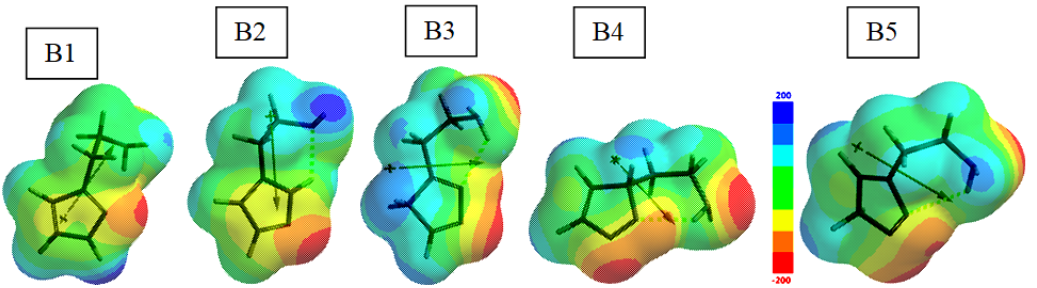


Figure 4. Electrostatic potential maps of the tautomers considered.

Table 2. Some thermo chemical values of the tautomers considered.

Tautomer	Hº	Sº (J/molº)	Gº
B1	-945540.5444	344.79	-945643.3442
B2	-945548.3737	342.30	-945650.4305
B3	-945451.1531	347.38	-945554.7275
B4	-945414.8919	344.96	-945517.7443
B5	-945429.1433	346.08	-945532.3291

Energies in kJ/mol.

Table 3 lists some energies of the tautomers considered where E, ZPE and EC stand for the total electronic energy, zero point vibrational energy and the corrected total electronic energy, respectively. As seen in the table all the tautomers considered are electronically stable and the stability order (in vacuum) is B2>B1>B3>B5>B4. Note that in tautomers B3-B5 lone-pair, lone-pair repulsive energy exists between the ring nitrogen atoms. Additionally, some steric effects should have arisen due to peculiar structure of each tautomer. The results reveal that aqueous energies of B1-B5 are -945976.09, -945980.46, -945895.05, -945837.00, -945860.23 kJ/mol., sequentially. It should be worth mentioning that both of B1 and B2 are aromatic structures however B2 is aquated better than B1.

Table 3. Some energies of the tautomers considered.

Tautomer	E	ZPE	E_C
B1	-945932.85	380.25	-945552.60
B2	-945942.58	382.56	-945560.02
B3	-945838.32	374.75	-945463.57
B4	-945802.94	376.13	-945426.81
B5	-945816.22	374.80	-945441.42

Energies in kJ/mol.

Figure 5 displays some of the molecular orbitals of the tautomers of interest. The HOMO, LUMO energies (ε_{HOMO} and ε_{LUMO}, respectively) and intermolecular orbital energy gap ($\Delta\varepsilon$) ($\Delta\varepsilon = \varepsilon_{LUMO}-\varepsilon_{HOMO}$) values of the tautomers are shown in Table 4. The data in the table reveal that the orders of the HOMO and LUMO energies are

B4<B3<B2<B5<B1 and B4<B5<B3<B2<B1, respectively. Whereas, the order of Δε values is B4<B5<B3<B2<B1. Thus, tautomer B4 is characterized with the lowest HOMO and LUMO energies. Whereas, B1 has the highest HOMO and LUMO energies. Note that tautomer B2 possesses lower HOMO and LUMO energies as compared to B1. The π-electron topology and hydrogen bonding occurring in B2 should have lowered both the frontier molecular orbitals of B2 with respect to B1.

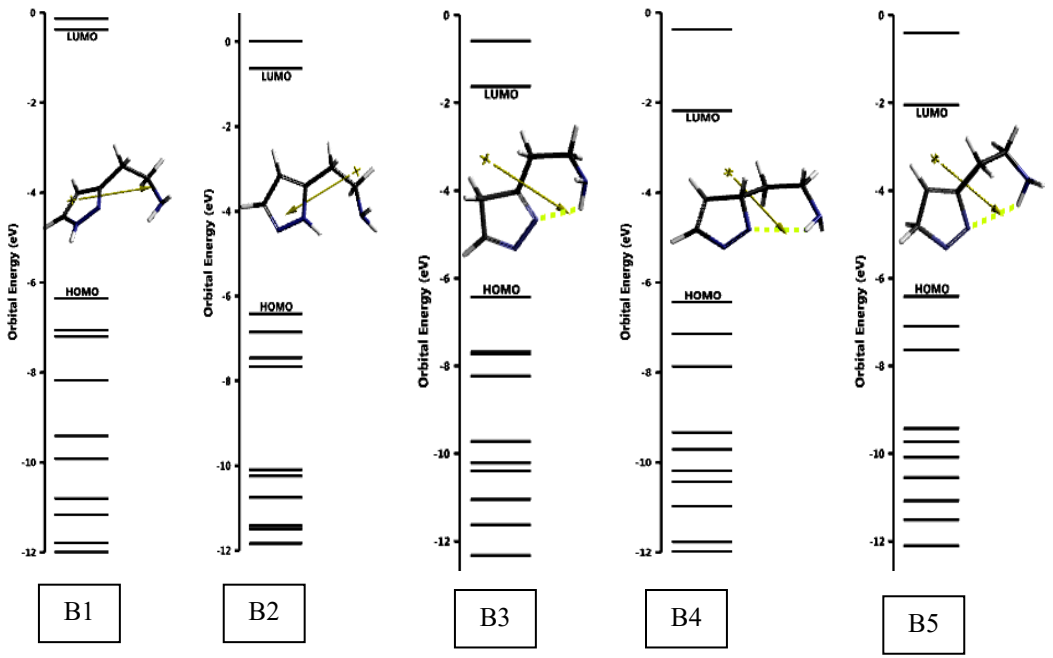


Figure 5. Some of the molecular orbitals of the tautomers of interest.

The distribution of inner molecular orbital energy levels also vary from tautomer to tautomer. Similar variations also exist for the NEXTLUMO energy levels.

Table 4. The HOMO, LUMO energies and Δν values of the tautomers considered.

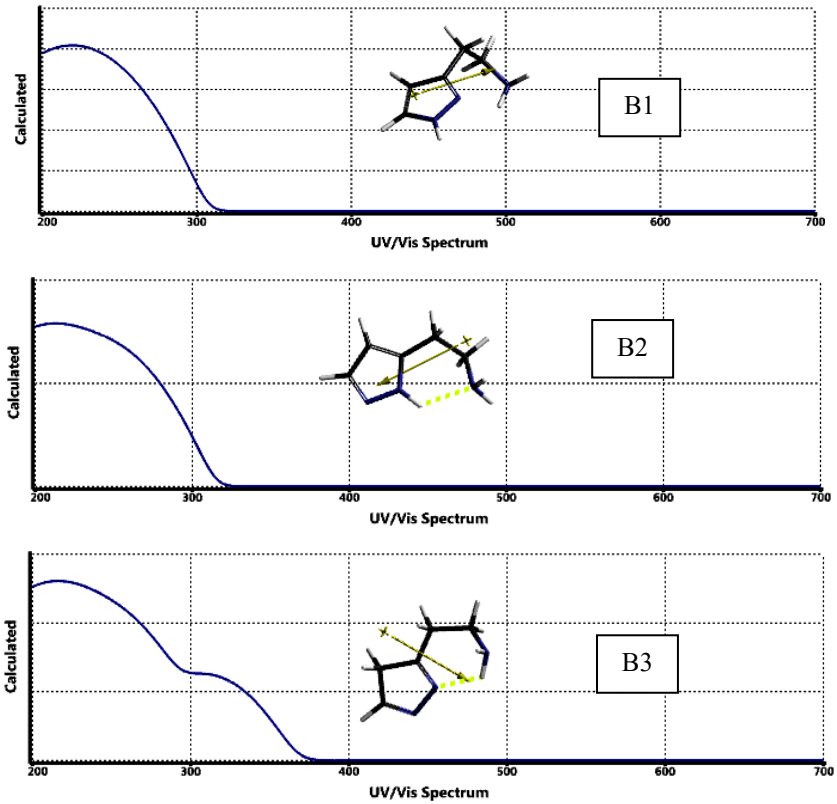
Tautomer	HOMO	LUMO	Δν
B1	-612.91	-36.52	576.39
B2	-619.52	-61.19	558.33
B3	-620.30	-156.70	463.60
B4	-620.90	-210.33	410.57
B5	-618.96	-197.00	421.96

Energies in kJ/mol.

Figure 6 shows the calculated UV-VIS spectra of the tautomers considered. As seen in the figure, tautomers B1, B2 and B3 absorb in the ultraviolet region only. Whereas B4 and B5 have some absorption in the visible region. Note that B4 and B5 have smaller interfrontier molecular orbital energy gap (Δν), so they exhibit some bathochromic shift to visible region as compared to the others. A shoulder in the spectrum of B3 progressively increases its intensity and becomes distinct peaks in the spectra of B4 and B5 (see Figure 6 and Table 5).

Table 5. λ_{max} values (nm) of the tautomers considered.

B1	B2	B3	B4	B5
217.53	211.89	213.72	223.99	231.35
		308.30	232.95	318.26
			375.92	363.20



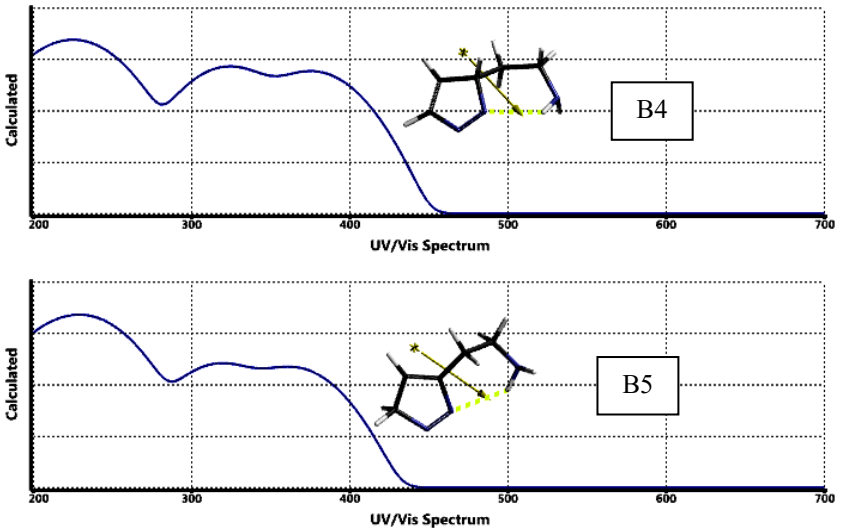


Figure 6. The calculated UV-VIS spectra of the tautomers considered.

NICS

To determine the local aromaticity of the pyrazole ring present in the tautomers considered, "nucleus-independent chemical shift" (NICS) values were obtained. Note that NICS is the computed value of the negative magnetic shielding at some selected point in space, generally at center of a ring or cage [39-51]. There are many review articles about NICS [43,44,50,51]. The calculated data so far have piled in the literature [39-51], have indicated that negative NICS values are associated with aromaticity. On the contrary, positive NICS values are associated with antiaromaticity while small NICS values are indicative of non-aromaticity. However, it is to be mentioned that although NICS approach has been proved to be an effective probe for the local aromaticity of individual rings of polycyclic systems a couple of contradictory results have been reported [48]. Table 6 shows the NICS(0) values of tautomers B1 and B2. The other tautomers included in the present treatment do not have cyclic π-conjugation to be considered for aromaticity calculations.

Table 6. The NICS(0) values of B1 and B2.

B1	B2
-12.6289	-12.5455

Pyrazole nucleus shows high degree of aromatic character. Therefore, tautomers B3-B5 are less likely to occur because they are no longer aromatic. Although, in the case of

unsubstituted pyrazole inter conversion of tautomers, occur readily [52], substituents on the ring may affect the equilibrium biasing for one of the tautomers.

4. Conclusion

Within the constraints of the theory and basis set employed, the present DFT treatment of betazole tautomers considered has indicated that in vacuum as well as in aqueous conditions, they have thermo chemically favorable formation values and are electronically stable. Some of them are not aromatic structures and they are characterized with less favorable G^o values and they are less stable compared to the ones in which the pyrazole ring remains intact. Tautomer B2 is found to be more favorable and more stable than B1. The calculated properties of the tautomers are highly dependent on their tautomeric form, such as their solvation energies, dipole moments, polar surface areas and log P values. Especially the log P values of the aromatic ones (B1 and B2) are strikingly different from each other. Their calculated UV-VIS spectra are similar each other and occur in the ultraviolet region only, whereas the others (B3-B5) mainly absorb in the ultraviolet but exhibit some bathochromic shift to the visible region.

References

[1] Windholz, M., & Budavari, S. (Eds.) (1983). The Merck Index (10th ed). Rahway, USA: Merck & Co. Inc.

[2] Sudhi, B.S., & Shaji, T.B. (2022). A review on heterocyclic compound pyrazole. *World Journal of Pharmaceutical Research*, *11*(12), 731-746.

[3] Eldebss, T.M.A., Eldebss, M.T.M., & Solimana, S.M.A. (2023). Utilities of pyrazolone and its derivative in heterocyclic synthesis and their biological applications. *Egypt. J. Chem., 66*(1), 453-478. https://doi.org/10.21608/EJCHEM.2022.123629.5521

[4] Boushey, H. A., & Holtzman, M. J. (1984). Histamine, serotonin, and the ergot alkaloids. In B. G. Katzung (Ed.), *Basic and clinical pharmacology*. Los Altos, California: Lange Medical Publications.

[5] Wruble, L.D., Cummins, A.J., Goldenberg, J., & Schapiro, H. (1967). The effect of intravenous histalog on gastric secretion in man. *Digestive Diseases and Sciences*, *12*(11), 1087-1090. PMID 6057052. S2CID 8990827. https://doi.org/10.1007/BF02233873

[6] Stoller, J.L., Holubitsky, I.B., Harrison, R.C., & Munro, A.I. (1970). Complications of the histalog test of gastric acid secretion. *Digestive Diseases and Sciences*, *15*(7), 647-651. PMID 4951403. S2CID 37678802. https://doi.org/10.1007/BF02236024

[7] Hammond, J.B., & Offen, W.W. (1988). Effect of nizatidine and cimetidine on betazole-stimulated gastric secretion of normal subjects: comparison of effects on acid, water, and pepsin. *Am. J. Gastroenterol*, *83*(1), 32-6. PMID 2892392.

[8] Jones, R.G., & Mann, M.J. (1953). New methods of synthesis of β-aminoethylpyrazole. *Journal of the American Chemical Society*, *75*(16), 4048-4052. https://doi.org/10.1021/ja01112a050

[9] Karrouchi, K., Radi, S., Ramli, Y., Taoufik, J., Mabkhot, Y.N., mailto:please_loginAl-aizari, F.A., & Ansar, M. (2018). Synthesis and pharmacological activities of pyrazole derivatives: A review. *Molecules*, *23*(1), 134. https://doi.org/10.3390/molecules23010134

[10] Romero-Fernandez, M., & Paradisi, F. (2021). Biocatalytic access to betazole using a one-pot multienzymatic system in continuous flow. *Green Chem*., *23*, 4594. https://doi.org/10.1039/D1GC01095F

[11] Llanos, O.L., Becker, S.N., & Thompson, J.C. (1978). Benign gastric ulcer in a patient with betazole-fast achlorhydria. *Arch Surg.*, *113*(2), 202-203. https://doi.org/10.1001/archsurg.1978.01370140092020

[12] Spitz, I.M., Novis, B.H., Ebert, R., Trestian, S., LeRoith, D., & Creutzfeldt, W. (1982). Betazole-induced GIP secretion is not mediated by gastric HCl. *Metabolism, 31*(4), 380-382. https://doi.org/10.1016/0026-0495(82)90114-7

[13] Ishimori, A., Sakurada, H., Kawamura, T., Yamagata, S., Miura, Y., Tsuda, K., & Yamagata, S. (1975). Comparison of dose-response curves between acid and pepsin to betazole hydrochloride in the dog with gastric fistula. *Gastroenterol Jpn.*, *10*, 221-224. https://doi.org/10.1007/BF02776656

[14] Laureta, H.C., Villamayor, C., & Calubiran, O.C. (1983). Determination of the dose of betazole that stimulates peak or maximum acid output among Filipinos. *The Journal of the Manila Medical Society*, *18*(2), 31-35.

[15] Karacadag, S., & Klotz, A.P.A. (1969). Comparative study of the effects of histamine and betazole hydrochloride on secretory capacity of the human stomach. *American Journal of Gastroenterology* (Springer Nature), *52*(5), 439-444.

[16] Marciano, T., & Wershil, B.K. (2007). The ontogeny and developmental physiology of gastric acid secretion. *Curr. Gastroenterol. Rep.*, *9*, 479-481. https://doi.org/10.1007/s11894-007-0063-7

[17] Kabi, A.K., Sravani, S., Gujjarappa, R., Garg, A., Vodnala, N., Tyagi, U., Kaldhi, D., Velayutham, R., Gupta, S., & Malakar, C.C. (2022). An introduction on evolution of azole derivatives in medicinal chemistry, overview on biological activities of pyrazole derivatives. In B. P. Swain (Ed.), *Nanostructured biomaterials*: *Materials horizons - from*

nature to nanomaterials. Singapore: Springer. https://doi.org/10.1007/978-981-16-8399-2_7

[18] Larina, L.I. (2018). Tautomerism and structure of azoles: Nuclear magnetic resonance spectroscopy. In E. F. V. Scriven & C. A. Ramsden (Eds.), *Advances in heterocyclic chemistry* (Vol. 124, pp. 233-321). New York: Academic Press. https://doi.org/10.1016/bs.aihch.2017.06.003

[19] Smeyers, Y.G., & Muñoz-Caro, C. (1989). Comparative CNDO/2 study of the molecular determinants for H2-receptor agonist activity in histamine and betazole agonist activity in histamine and betazole. *European Journal of Medicinal Chemistry*, *24*(4), 411-414. https://doi.org/10.1016/0223-5234(89)90085-8

[20] Taherpour, A.A., Chegeni, M.M.F., Khodaei, M.M., & Tamasoki, N. (2017). A first principle DFT study of solvent effects on metiamide tautomers and imaginary interactions with H2-receptors. *J. Iran Chem. Soc.*, *14*, 1613-1632. https://doi.org/10.1007/s13738-017-1102-4

[21] Taherpour, A., & Rahimizadeh, R. (2016). Study of solvent effects on structural and conformational properties of cimetidine tautomers. *Med. Chem. Res.*, *25*, 2042-2057. https://doi.org/10.1007/s00044-016-1612-0

[22] Stewart, J.J.P. (1989). Optimization of parameters for semi empirical methods I. *J. Comput. Chem*., *10*, 209-220. https://doi.org/10.1002/jcc.540100208

[23] Stewart, J.J.P. (1989). Optimization of parameters for semi empirical methods II. *J. Comput. Chem*., *10*, 221-264. https://doi.org/10.1002/jcc.540100209

[24] Leach, A.R. (1997). *Molecular modeling*. Essex: Longman.

[25] Kohn, W., & Sham, L.J. (1965). Self-consistent equations including exchange and correlation effects. *Phys. Rev*., *140*, 1133-1138. https://doi.org/10.1103/PhysRev.140.A1133

[26] Parr, R.G., & Yang, W. (1989). *Density functional theory of atoms and molecules*. London: Oxford University Press.

[27] Becke, A.D. (1988). Density-functional exchange-energy approximation with correct asymptotic behavior. *Phys. Rev. A*, *38*, 3098-3100. https://doi.org/10.1103/PhysRevA.38.3098

[28] Vosko, S.H., Wilk, L., & Nusair, M. (1980). Accurate spin-dependent electron liquid correlation energies for local spin density calculations: a critical analysis. *Can. J. Phys.*, *58*, 1200-1211. https://doi.org/10.1139/p80-159

[29] Lee, C., Yang, W., & Parr, R.G. (1988). Development of the Colle-Salvetti correlation

energy formula into a functional of the electron density. *Phys. Rev. B*, *37*, 785-789. https://doi.org/10.1103/PhysRevB.37.785

[30] SPARTAN 06 (2006). Wavefunction Inc. Irvine CA, USA.

[31] Gaussian 03, Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Montgomery, Jr., J.A., Vreven, T., Kudin, K.N., Burant, J.C., Millam, J.M., Iyengar, S.S., Tomasi, J., Barone, V., Mennucci, B., Cossi, M., Scalmani, G., Rega, N., Petersson, G.A., Nakatsuji, H., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Klene, M., Li, X., Knox, J.E., Hratchian, H.P., Cross, J.B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev, O., Austin, A.J., Cammi, R., Pomelli, C., Ochterski, J.W., Ayala, P.Y., Morokuma, K., Voth, G.A., Salvador, P., Dannenberg, J.J., Zakrzewski, V.G., Dapprich, S., Daniels, A.D., Strain, M.C., Farkas, O., Malick, D.K., Rabuck, A.D., Raghavachari, K., Foresman, J.B., Ortiz, J.V., Cui, Q., Baboul, A.G., Clifford, S., Cioslowski, J., Stefanov, B.B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Martin, R.L., Fox, D.J., Keith, T., Al-Laham, M.A., Peng, C.Y., Nanayakkara, A., Challacombe, M., Gill, P.M.W., Johnson, B., Chen, W., Wong, M.W., Gonzalez, C., & Pople, J.A., Gaussian, Inc., Wallingford CT, 2004.

[32] Reutov, O. (1970). *Theoretical principles of organic chemistry*. Moscow: Mir Pub.

[33] Anslyn, E.V., & Dougherty, D.A. (2006). *Modern physical organic chemistry*. Sausalito, California: University Science Books.

[34] Betazole. *CAS Common Chemistry*. CAS, a division of the American Chemical Society, n.d. https://commonchemistry.cas.org/detail?cas_rn=105-20-4 (retrieved 2023-06-14) (CAS RN: 105-20-4).

[35] J-GLOBAL. http://jglobal.jst.go.jp/en/redirect?Nikkaji_No=J5.041E

[36] PubChem. https://pubchem.ncbi.nlm.nih.gov/substance/?source=15745&sourceid=8041967-188166155

[37] Hitchcock, S.A., & Pennington, L.D. (2006). Structure-brain exposure relationships. *J. Med. Chem*., *49* (26), 7559-7583. PMID: 17181137. https://doi.org/10.1021/jm060642i

[38] Shityakov, S., Neuhaus, W., Dandekar, T., & Förster, C. (2013). Analysing molecular polar surface descriptors to predict blood-brain barrier permeation. *International Journal of Computational Biology and Drug Design*, *6*(1-2), 146-56. PMID: 23428480. https://doi.org/10.1504/IJCBDD.2013.052195

[39] Minkin, V.I., Glukhovtsev, M.N., & Simkin, B.Y. (1994). *Aromaticity and antiaromaticity: Electronic and structural aspects*. New York: Wiley.

[40] Schleyer, P.R., & Jiao, H. (1996). What is aromaticity?. *Pure Appl. Chem*., *68*, 209-218. https://doi.org/10.1351/pac199668020209

[41] Schleyer, P.R. (2001). Introduction: aromaticity. *Chem. Rev*., *101*, 1115-1118. https://doi.org/10.1021/cr0103221

[42] Cyranski, M.K., Krygowski, T.M., Katritzky, A.R., & Schleyer, P.R. (2002). To what extent can aromaticity be defined uniquely?. *J. Org. Chem*., *67*, 1333-1338. https://doi.org/10.1021/jo016255s

[43] Chen, Z., Wannere, C.S., Corminboeuf, C., Puchta, R., & Schleyer, P. von R. (2005). Nucleus independent chemical shifts (NICS) as an aromaticity criterion. *Chem. Rev*., *105*(10), 3842-3888. https://doi.org/10.1021/cr030088

[44] Gershoni-Poranne, R., & Stanger, A. (2015). Magnetic criteria of aromaticity. *Chem., Soc.Rev*., *44*(18), 6597-6615. https://doi.org/10.1039/C5CS00114E

[45] Dickens, T.K., & Mallion, R.B. (2016). Topological ring-currents in conjugated systems. *MATCH Commun. Math. Comput. Chem*., *76*, 297-356.

[46] Stanger, A. (2010). Obtaining relative induced ring currents quantitatively from NICS. *J. Org. Chem*., *75*(7), 2281-2288. https://doi.org/10.1021/jo1000753

[47] Monajjemi, M., & Mohammadian, N.T. (2015). S-NICS: An aromaticity criterion for nano molecules. *J. Comput. Theor. Nanosci*., *12*(11), 4895-4914. https://doi.org/10.1166/jctn.2015.4458

[48] Schleyer, P.R., Maerker, C., Dransfeld, A., Jiao, H., & Hommes, N.J.R.E. (1996). Nucleus independent chemical shifts: a simple and efficient aromaticity probe. *J. Am. Chem. Soc*., *118*, 6317-6318. https://doi.org/10.1021/ja960582d

[49] Corminboeuf, C., Heine, T., & Weber, J. (2003). Evaluation of aromaticity: A new dissected NICS model based on canonical orbitals. *Phys. Chem. Chem. Phys.*, *5*, 246-251. https://doi.org/10.1039/B209674A

[50] Stanger, A. (2006). Nucleus-ındependent chemical shifts (NICS): Distance dependence and revised criteria for aromaticity and antiaromaticity. *The Journal of Organic Chemistry*, *71*(3), 883-893. https://doi.org/10.1021/jo051746o

[51] Chen, Z., Wannere, C.S., Corminboeuf, C., Puchta, R., & Schleyer, P.R. (2005). Nucleus-ındependent chemical shifts (NICS) as an aromaticity criterion. *Chemical Reviews*, *105*(10), 3842-3888. https://doi.org/10.1021/cr030088+

[52] Katritzky, A.R., & Lagowski, J.M. (1971). *The principles of heterocyclic chemistry*, London: Chapman and Hall.