

Hemihexaphyrazine and Thiadiazole Annulated Hemihexaphyrazine: A Theoretical Insight into Aromaticity and Energetics of Hydrogen Bonding

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Seventeen tautomeric structures of hemihexaphyrazine were considered using DFT in B3LYP/pcseg-2 approximation. The tautomer of D_{3h} symmetry was found to be the most energetically favorable, and transformations into other tautomers are practically forbidden by high energy barriers (more than 50 kJ·mol⁻¹). The energetics of hydrogen bonding was estimated by NBO and QTAIM calculations and the preferable D_{3h} tautomer turned out to possess the lowest total hydrogen bond stabilization energy, according to the results of the NBO-analysis. Aromaticity of the D_{3h} and C_{3h} tautomers of hemihexaphyrazine and its thiadiazole annulated analogue was described with use of three popular descriptors: NICS, HOMA and FLU. Tautomeric preference and structural features of the both molecules were found to be very similar.

Keywords: Hemihexaphyrazine, aromaticity, hydrogen bonding, NBO-analysis, QTAIM.

Гемигексафиазин и тиадiazол–аннелированный гемигексафиазин: теоретическое исследование ароматичности и энергетики водородных связей

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С помощью DFT расчетов в приближении B3LYP/pcseg-2 изучены семнадцать таутомеров гемигексафиазина. Таутомер симметрии D_{3h} является наиболее энергетически выгодным, причем его превращения в другие таутомеры практически невозможны из-за высоких энергетических барьеров (более 50 кДж/моль). Энергия водородных связей была оценена с помощью расчетов в приближениях NBO и QTAIM. Согласно результатам NBO-анализа, суммарная энергия внутримолекулярных водородных связей имеет наименьшее значение для наиболее энергетически выгодного D_{3h} таутомера молекулы. Ароматичность D_{3h} и C_{3h} таутомеров гемигексафиазина и его тиадiazол–аннелированного аналога была описана с использованием трёх критериев ароматичности: NICS, HOMA и FLU. Согласно результатам расчётов, молекулы обнаруживают сходные тенденции в изменении суммарной энергии внутримолекулярных водородных связей и ароматичности.

Ключевые слова: Гемигексафиазин, ароматичность, водородная связь, NBO-анализ, QTAIM.

Introduction

Investigations of the molecular structure and tautomeric preference of macroheterocyclic systems have been the subject of the many recent studies.^[1-7] Among a huge number of macrocycles, hemihehexaphyrazines of ABABAB-type attract a great interest due to their unusually high symmetrical structures,^[4-6] expanded coordination cavity with enormous potential in coordination chemistry^[8-11] and catalysis,^[12] and molecular level information storage.^[6] In our recent work^[13] a study of tautomeric preference and intramolecular hydrogen bonding was performed for the thiadiazole annulated hemihehexaphyrazine (**TDAHHp**, Scheme 1). According to the results of the DFT calculations, **TDAHHp** was determined to have the single energetically favourable tautomer of D_{3h} symmetry, while the other structures were more than 39 kJ·mol⁻¹ higher in energy. An attempt was made to explain this preference by the presence of six intramolecular hydrogen bonds $N_i \cdots H$ inside coordination cavity in the case of the D_{3h} structure, since all the other tautomers contained less than six bonds.

However, the calculations of the total hydrogen bond stabilization energy ($E_{HB,tot}$) performed in the framework of the NBO-analysis of the electron density distribution drew the contrary picture: less number of stronger hydrogen bonds in the other tautomers provide their structures with larger stabilization energies as compared to the preferable D_{3h} structure. The calculations of $E_{HB,tot}$ with use of QTAIM approach resulted in the opposite trend: the D_{3h} structure of **TDAHHp** was found to possess the largest stabilization energy among the considered tautomers, however, the difference between the lowest and the largest $E_{HB,tot}$ values was 6 times less as compared to the quantity of same kind calculated from the NBO analysis. These contradictive results did not explain the pronounced preference of the D_{3h} structure.

This work expands our investigation of **TDAHHp** in two ways: the previously found contradiction between NBO and QTAIM estimations of hydrogen bond energies is examined for the analogous tautomers of the parent hemihehexaphyrazine (**HHp**, Scheme 1) mac-

rocycle, and another powerful factor that can influence the tautomeric preference, namely, aromaticity is assessed for both **TDAHHp** and **HHp** molecules.

Computational details

DFT calculations for 17 possible NH-tautomers of **HHp** were performed with use of Gaussian 09 program package.^[14] The calculations were carried out using B3LYP^[15-17] functional and pcseg-2^[18] basis set (C,N,H,S) taken from the EMSL BSE library. Planar models of the tautomers (Figure S1) were optimized under D_{3h} (**HHp**), C_{3h} (**3PT-1**), C_{2v} (**2PT-1**, **2PT-7**, **2PT-8**) and C_s (**1PT-1**, **1PT-2**, **1PT-3**, **2PT-2**, **2PT-3**, **2PT-4**, **2PT-5**, **2PT-6**, **2PT-9**, **3PT-2**, **3PT-3**, **3PT-4**) symmetry constraints. Vibrational frequencies were calculated in the harmonic approximation for all the optimized structures. The abbreviations of the tautomers reflect “proton(s) transfer” (**PT**) from the main **HHp** structure, e.g., the structures **1PT-1** and **1PT-2** can be obtained from the main **HHp** structure by “migration” of one hydrogen from atom N of an isoindole fragment to atom N_i of a thiadiazole fragment, etc.

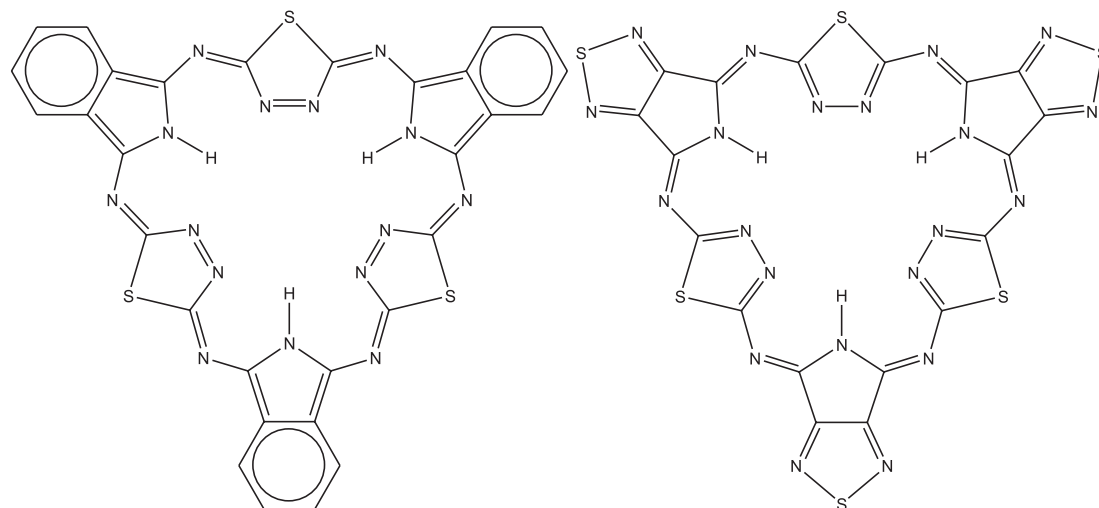
The search of transition states between the structures corresponding to local minima on the PES was performed using the Synchronous Transit-Guided Quasi-Newton (STQN) Method^[19] requested by QST3 keyword.

The natural bond orbital (NBO) analysis was performed as it is implemented in Gaussian 09.^[20]

Quantitative QTAIM (Quantum Theory of Atoms in Molecules) analysis was performed using AIMAll software package.^[21]

Aromaticity of the main D_{3h} -structures of **HHp**, its thiadiazole annulated analogue (**TDAHHp**) and their **3PT-1** tautomers was estimated with use of NICS,^[22] HOMA^[23] and FLUJ^[24,25] descriptors. NICS(0) values were calculated at the centers of the cyclic fragments and NICS(1) – at points 1 Å above the ring centers. The values of HOMA criterion were calculated for the optimized structures as proposed in the ref.^[23] FLU descriptors were estimated from the results of the AIM calculations according to the formulae proposed by E. Matito *et al.*^[24] It should be noted that the $\delta_{ref}(C-S) = 1.29$ was taken as $\delta(C-S)$ in the aromatic thiophene molecule calculated at B3LYP/pcseg-2 level. The value of $\delta_{ref}(N-S) = 1.30$ was taken as $\delta(N-S)$ in 1,2,5-thiadiazole calculated at the same level.

Molecular models were visualized with use of Chemcraft program.^[26]



Scheme 1. Hemihehexaphyrazine (**HHp**, left) and thiadiazole annulated hemihehexaphyrazine (**TDAHHp**, right).

Results and Discussion

NH-Tautomerism and Energetics of Hydrogen Bonding in HHp and TDAHHp

According to the results of the calculations, the structure of **HHp** of D_{3h} symmetry corresponds to the global minimum on the PES. The local minima (**1PT-1**, **2PT-1**, **2PT-3**, **2PT-7**, **3PT-1**, **3PT-4**, see Figure 1) are more than 45 kJ·mol⁻¹ higher

in energy (see Table S1). Another NH-tautomers were found to correspond to saddle points on the PES.

Relative energies of the most energetically favorable tautomers of **HHp** demonstrate the similar trend as those previously reported for the **TDAHHp** molecule.^[13]

The barriers were calculated by to be very high (more than 50 kJ·mol⁻¹, Figure 2), therefore both **HHp** and **TDAHHp** should only adopt the lowest in energy D_{3h} structures.

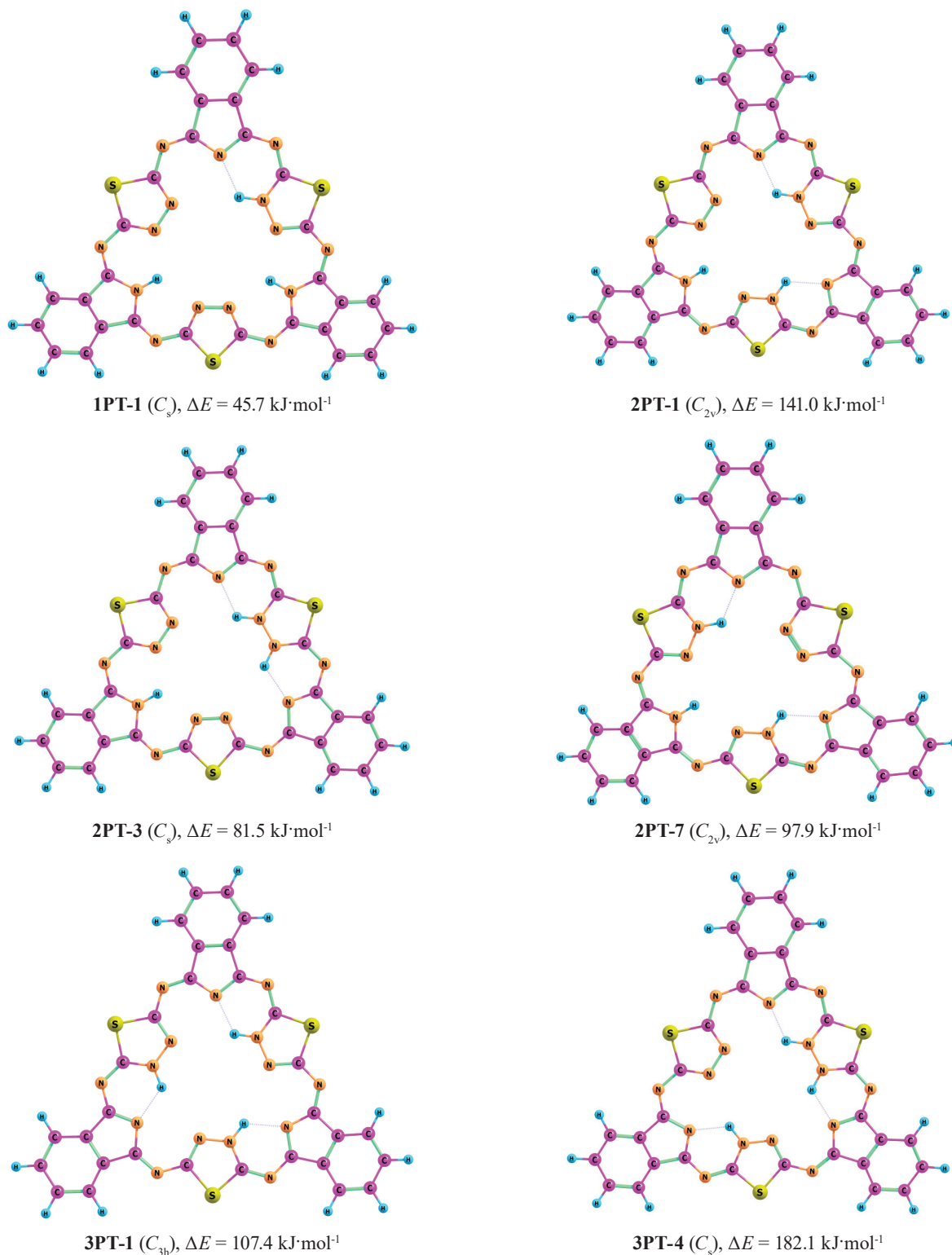


Figure 1. Structures of the tautomers of **HHp** corresponding to the local minima on the PES, and their energies relative to the D_{3h} structure (Scheme 1).

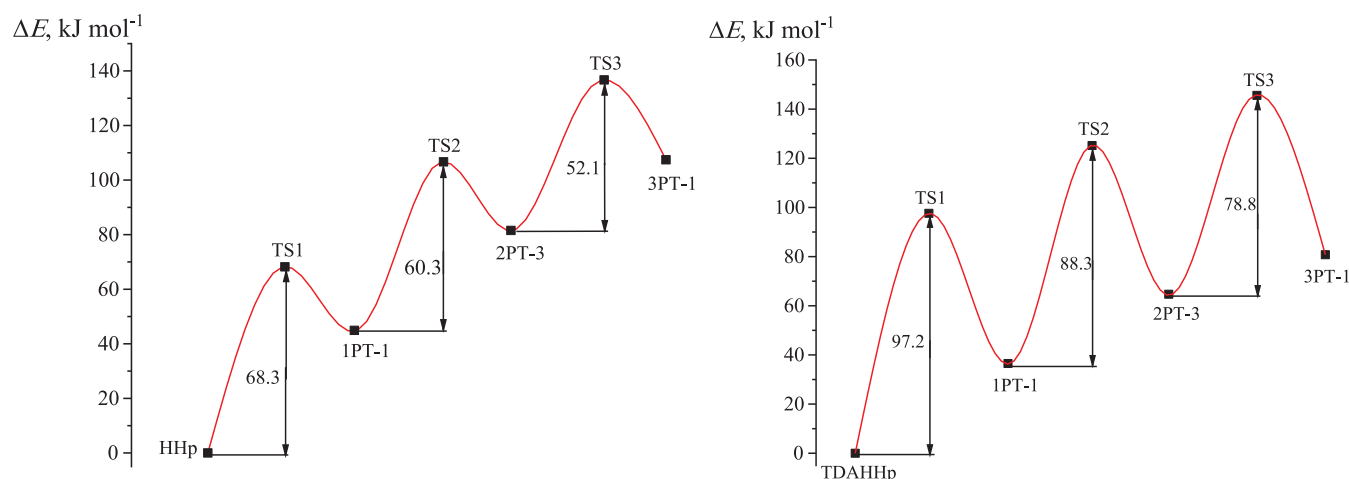


Figure 2. Energy barriers for the proton transfer processes in **HHp** and **TDAHHp** estimated from QST3 calculations.

The energies of the intramolecular hydrogen bonds were estimated based on the NBO-analysis as the energies of donor-acceptor interactions between the lone pairs (LPs) of the N_t atoms and $\sigma^*(\text{N-H})$ antibonding orbitals. The total energy $E_{\text{sum}}^{(2)}[\text{LP}(\text{N}) \rightarrow \sigma^*(\text{N-H})]$ was found to be the largest in the case of **3PT-1** tautomers of **HHp** and **TDAHHp** (see Table 1). Another possible way using AIM results to estimate the energy of a hydrogen bond was suggested by Espinosa *et al.*^[27] They proposed an equation, connecting this energy with the potential energy density $V(\mathbf{r}_{\text{CP}})$ calculated at a bond critical point: $E_{\text{HB}} = 0.5V(\mathbf{r}_{\text{CP}})$. The calculations for the series of the tautomers of **HHp** based on the results of QTAIM calculations demonstrated the opposite trend in the values of E_{HB} as compared to the NBO results. However, the difference in the total hydrogen bond energies between the main D_{3h} structure and **3PT-1** tautomer is much larger according to the NBO calculations as compared to QTAIM (see Figure 3). Therefore, hydrogen bonding is not responsible for the found preference of the D_{3h} structures of **HHp** and **TDAHHp**: three strong H-bonds in the **3PT-1** tautomers provide their structures with larger total stabilization energies as compared to six weak N...H contacts occurring in the most favourable D_{3h} tautomers. The trends shown in Figure 3 are similar for both **HHp** and **TDAHHp**. Therefore, the replacement of the benzene ring in **HHp** by thiadiazole

ring (in **TDAHHp**) does not influence the interactions inside macrocyclic cavity.

Macrocyclic Core of TDAHHp and HHp: Aromatic or Not?

Pronounced stability of D_{3h} structures of **TDAHHp** and **HHp** might be supposed to be caused by the aromatic properties of their macrocyclic core. In order to examine this hypothesis, we applied the well-known aromaticity criteria HOMA and NICS and the recently developed FLU descriptor to the tautomers with the smallest and the largest numbers of the intramolecular hydrogen bonds. The results of the calculations are listed in Table 2.

According to the results of the calculations, the values of the aromaticity indices HOMA, NICS and FLU calculated in the centers of the macrocycles do practically not depend on the nature of the annulated ring (either benzene in **HHp**, or thiadiazole in **TDAHHp**). However, aromaticity of the macrocycle increases in the case of **3PT-1** tautomer as compared to the main D_{3h} structures according to the values of all the descriptors examined. One can also note a decrease of aromaticity of a thiadiazole ring (thiadiazole A in the case of **TDAHHp**) in **3PT-1** tautomers as

Table 1. Relative energies of the tautomers of **HHp** and **TDAHHp** and total hydrogen bond stabilization energies estimated from NBO and QTAIM calculations.

Model	HHp	1PT-1	2PT-3	3PT-1
ΔE , kJ·mol ⁻¹	0	45.7	81.5	107.4
$E_{\text{sum}}^{(2)}[\text{LP}(\text{N}) \rightarrow \sigma^*(\text{N-H})]$, kJ·mol ⁻¹	97.7	117.1	141.8	160.8
$E_{\text{HB, total}}$, kJ·mol ⁻¹	112.6	111.1	110.6	109.1
Model	TDAHHp	1PT-1	2PT-3	3PT-1
ΔE , kJ·mol ⁻¹	0	39.2	68.8	88.7
$E_{\text{sum}}^{(2)}[\text{LP}(\text{N}) \rightarrow \sigma^*(\text{N-H})]$, kJ·mol ⁻¹	92.6	106.1	125.5	138.8
$E_{\text{HB, total}}$, kJ·mol ⁻¹	107.7	104.6	102.8	100.0
Number of H-bonds	6	5	4	3

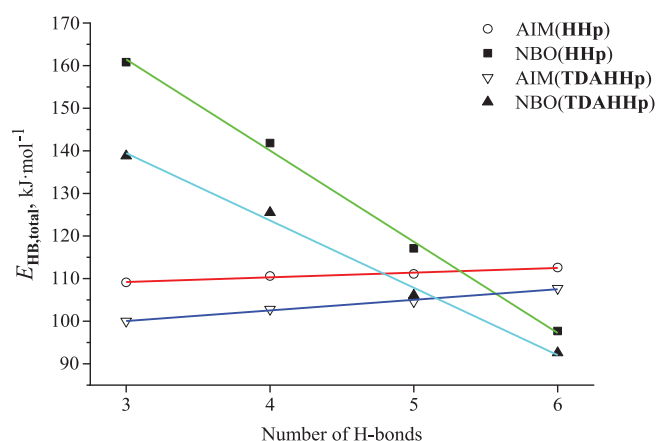


Figure 3. Trends in the total hydrogen bond stabilization energy in the series of tautomers of **HHp** and **TDAHHp** according to the NBO and QTAIM calculations.

hydrogen atoms being bonded to the N atoms of the isoin-dole rings. The other tautomers are more than 45 kJ·mol⁻¹ higher in energy and transitions between the tautomers in the gas phase were calculated to be practically forbidden by the large barriers. Interestingly, the total stabilization energy of the intramolecular hydrogen bonds, estimated from the NBO calculations, was found to be the lowest in the case of the most energetically favorable D_{3h} tautomer. Another reason of stabilization of the D_{3h} structure might be connected with its possible aromatic properties. However, according to the values of HOMA and FLU aromaticity descriptors, the structure of C_{3h} symmetry should possess more pronounced aromatic properties as compared to the main D_{3h} tautomer. At the same time, positive values of the NICS criterion calculated in the center of the macrocycle indicate the absence of aromaticity. The structural features were found to be the same for hemihexaphyrazine and its thiadiazole annulated analogue. Therefore, the replacement of the benzene ring in **HHp** by thiadiazole

Table 2. Aromaticity criteria NICS, HOMA and FLU for **HHp** and **TDAHHp** and their **3PT-1** tautomers.

	NICS(0)	NICS(1)	HOMA	FLU		NICS(0)	NICS(1)	HOMA	FLU
HHp (D_{3h})					TDAHHp (D_{3h})				
Center	+1.37	+0.83	0.864	0.022	Center	+1.52	+0.96	0.833	0.024
Thiadiazole	-8.39	-7.23	0.772	0.010	Thiadiazole A	-8.68	-7.60	0.801	0.009
Pyrrole	+1.72	-0.68	0.208	0.063	Pyrrole	+4.38	+0.04	0.167	0.073
Benzene	-7.06	-8.94	0.991	0.001	Thiadiazole B	-11.04	-10.43	–	0.008
3PT-1 (C_{3h})					3PT-1 (C_{3h})				
Center	+1.10	+0.78	0.934	0.012	Center	+1.13	+0.80	0.923	0.013
Thiadiazole	-7.83	-4.88	0.566	0.020	Thiadiazole A	-8.09	-5.18	0.716	0.019
Pyrrole	+6.43	+0.88	0.280	0.029	Pyrrole	+9.09	+1.21	0.047	0.058
Benzene	-6.53	-8.45	0.985	0.001	Thiadiazole B	-9.59	-9.43	–	0.010

compared to the D_{3h} structures, that reflects its increased involvement into macrocyclic conjugation system. Experimental evidences of the non-aromatic character of **HHp** were found in.^[7]

At the same time, the obtained results indicate a contradiction between NICS criterion, on the one side, and HOMA and FLU descriptors on the other, concerning aromaticity of the macrocyclic core in the considered tautomers of **HHp** and **TDAHHp**. Positive NICS values calculated in the centers of the macrocycles reflect the absence of aromaticity, while the values of HOMA and FLU are close to that of the aromatic compounds, especially in the case of **3PT-1** tautomers.

Conclusions

Tautomeric preference of hemihexaphyrazine was studied for the first time by DFT calculations. The structure corresponding to the global minimum on the PES possesses the structure of D_{3h} symmetry with three inner

ring (in **TDAHHp**) does not influence the interactions inside macrocyclic cavity.

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