

Imidazole and Its Saturated Derivatives Vs Pyrazole And Its Saturated Derivatives: A Computational Study on Relative Stability

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Abstract

Possible structures of imidazole, pyrazole, and their semi saturated and fully saturated derivatives have been studied at the DFT and ab initio computational levels. Calculations have been performed using several computational schemes (BLYP, PBE0, CAM-B3LYP, wB97XD, M06, MP2, CBS-QB3, and G4 methods have been employed) and the 6-311++G** basis set. The most stable structures for each group of studied compounds (tautomers of native imidazole and pyrazole, tautomers of their semi saturated derivatives, and fully saturated derivatives) have been determined. In general species with imidazole ring are more stable than those with pyrazole one. The discussion of this phenomenon origin, especially the influence of aromaticity as well as distributions of total charge and energy among atoms are thoroughly discussed.

Keywords: Imidazole, Pyrazole, Stability, Quantum Chemistry, Computational Chemistry

Introduction

Five-membered heterocycles with two nitrogen atoms in the ring, i.e. imidazole and pyrazole exist as parts of many compounds, among them these crucial for biology. These compounds and their derivatives have also numerous applications, most important in pharmacology but also in other branches of industry [1-3]. Due to its importance pyrazole, imidazole and their derivatives are still the topics of endless research. One of the basic phenomena associated with imidazoles and pyrazoles is their tautomerism, or rather prototropy, a form of tautomerism in which the two forms differ only in the position of a proton and the transfer of a proton is reversible [4]. That's why, arise a question in which tautomeric structure is dominant and if only one tautomeric structure should be detectible or more structures can be observed experimentally. This topic was studied computationally for native imidazole and closely related compounds in several papers [5-9]. It was recognized that both systems, imidazole and pyrazole, exist in their delocalized – aromatic forms. However, the possibility of non-aromatic structures existence was discussed [10-11]. The influence of the substituent effect on the relative stability of substituted pyrazoles and imidazoles was also investigated [12]. As the most stable structures of studied systems were detected previously, the main topic of this work is rather deeper discussion and looking for an explanation of why one tautomeric structure is more stable than another one. The stress was also pointed toward a problem which system, imidazole or pyrazole, is more stable and why. We also calculated energies and discuss reasons for relative stabilities of semi saturated and fully saturated imidazole and pyrazole derivatives.

Materials and Methods

The geometries of the molecules have been fully optimized with several theoretical approaches. We used several hybrid HF/DFT functionals: B3LYP [13-14], CAM-B3LYP [15], PBE0 [16], wB97XD [17] and M06 [18]. These approaches are ones of the most popular functionals. Some of them have additional useful properties like long-range or dispersion corrections. We used also classical second-order perturbation approach (MP2 [19]), as well as the Complete Basis Set (CBS-QB3 [20]) and Gaussian-4 (G4 [21]) methods for computing very accurate energies. For all calculations, the 6-311++G** basis set [22-23] has been employed. Frequency calculations have been carried out at the same computational level to confirm that the structures obtained correspond to energetic minima. All energetical and structural calculations have been performed by the G09 software [24]. The electron density of the molecules has been analyzed with the AIM methodology [25] using the AIMAll program

[26]. AIM method has been used to split total charges and total electronic energies into atomic contributions. Then relative atomic energies, very useful to understanding why one tautomer is more stable than another one, have been calculated. The energy of each atom in the most stable tautomer is subtracted from the energies of their counterparts in other tautomers. Thus a positive value of relative atomic energy denotes higher stability of the atom in the most stable tautomer, whereas a negative value denotes a higher stability of the particular atom in another tautomer, with higher total energy [27]. HOMA (Harmonic Oscillator Model of Aromaticity) index has been used to evaluate the aromaticity level of studied compounds. [28-29] It is a very popular index [30-31] because it combines two important features. It gives reliable results and is easy to use. To calculate the HOMA index, a simple analytical formula is used, and only bond lengths in the ring being tested (which are determined during the optimization of geometry) are necessary. The HOMA index value for a fully aromatic ring is equal to 1.0 while 0.0 value is characteristic for a nonaromatic system. Negative HOMA index value suggests the antiaromaticity of the studied ring.

Results and Discussion

All considered in this work structures are presented in Fig. 1. They represent all possible structures for the five-membered carbon ring with two carbons replaced by nitrogen atoms. The set of studied compounds can be divided into three groups: unsaturated (i.e. tautomers of pyrazole and imidazole), semi saturated (tautomers of imidazole and pyrazole in which one double bond has been transformed into a single one by addition of two hydrogen atoms) and fully saturated structures (one structure for each type of studied heterocyclic system) where both double bonds are hydrogenated.

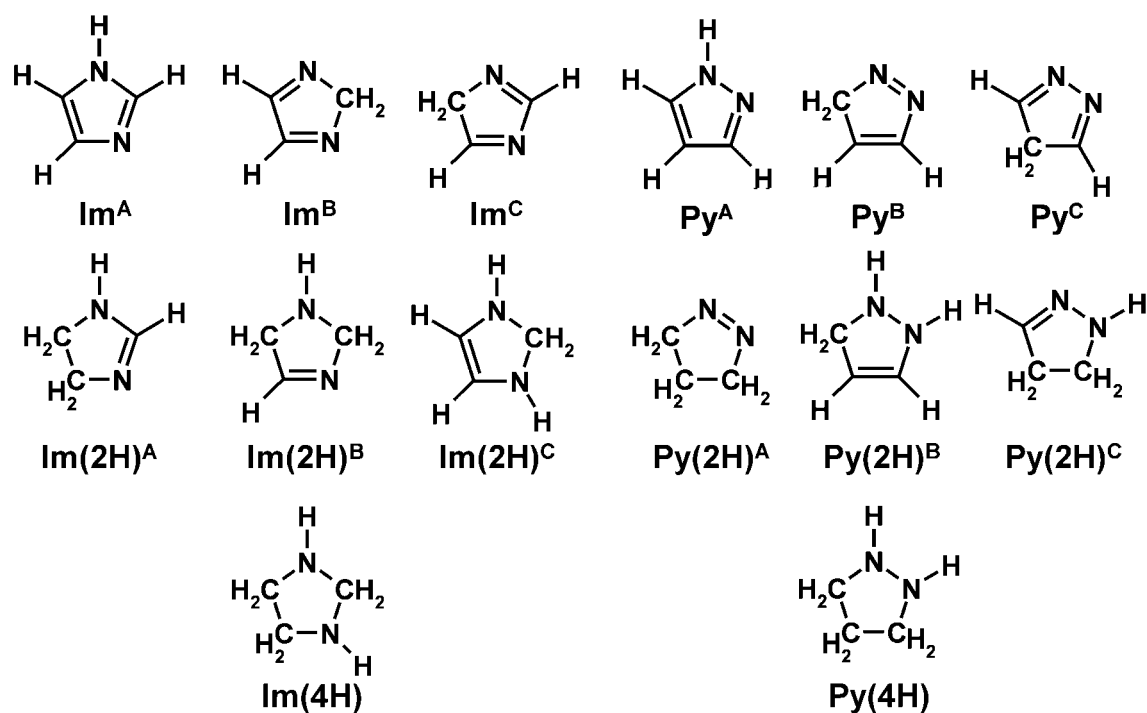


Fig. 1 Considered in this work tautomers of imidazole, pyrazole, and their saturated derivatives.

Non-saturated compounds

There are three tautomers of pyrazole and imidazole considered in this study, They are labelled as **Im^A**, **Im^B**, **Im^C** for imidazole and **Py^A**, **Py^B**, **Py^C** for pyrazole, see Fig. 1. The equilibrium structures of these tautomers are presented in Fig. 2.

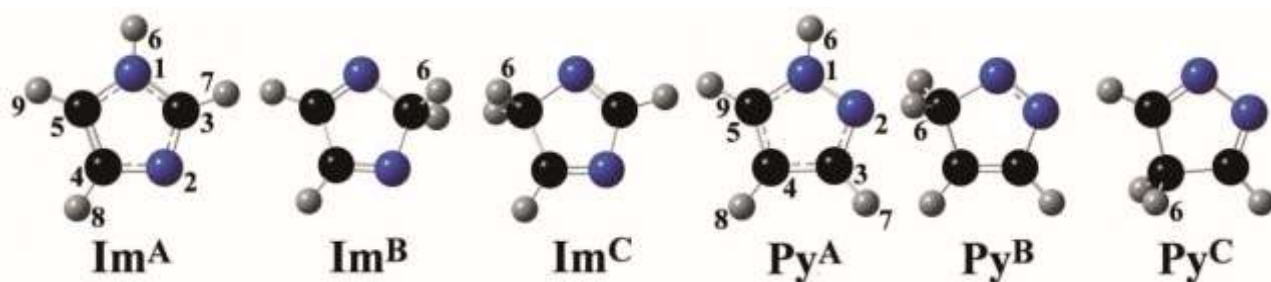


Fig. 2 Optimized structures (MP2/6-311++G level) and atom numbering scheme of imidazole and pyrazole tautomers (within a particular set of tautomers only numbers of moveable hydrogens are repeated).**

As it was expected, in the case of imidazole as well as pyrazole the most stable tautomeric structures are these with the NH group, **Im^A** and **Py^A**, respectively. Bonding a hydrogen to the nitrogen atom opens the possibility to have no methylene group in the ring, in a consequence no breaks in the electron delocalization over the whole ring. All other tautomers, in which the methylene group is formed, have significantly higher energies. The second tautomer of imidazole in the energetic order has the methylene group between nitrogen and carbon atoms (**Im^C**, with an exception for the MP2 method where the energy of the **Im^B** structure is slightly lower) and in tautomer, with the highest energy, the methylene group is positioned in the ring between two nitrogen atoms (**Im^B**). So, the increase of energy is observed if the methylene group is located closer to nitrogen atoms. Pyrazole tautomers follow this rule. In the pyrazole tautomer with medium energy, the methylene group is as far as possible from nitrogen atoms (**Py^C**), while in the least stable tautomer the CH₂ is adjacent to a nitrogen atom (**Py^B**). In both cases, imidazole and pyrazole, the energy gap between the structure with the lowest energy and next tautomer are high (about 60 kJ/mol for imidazole system and about 100 kJ/mol in case of pyrazole). Thus, only tautomers with the lowest energies **Im^A** and **Py^A** can be observed experimentally. The **Im^A** structure has the lowest energy among all imidazole's and pyrazole's tautomers. The next in the energetic order is the **Py^A** structure (about 45 kJ/mol higher energy). The middle energy range belongs to two imidazole tautomers, **Im^C** and **Im^B**, between which energy differences are small in general, and sometimes even different methods provide different energy order for these two structures). Two pyrazole tautomers **Py^B** and **Py^C** are the least stable structures, however, the **Py^C** tautomer is over a dozen kJ/mol more stable than **Py^B**. The full energetic order of pyrazole and imidazole tautomers is as follow: **Im^A << Py^A << Im^C ≈ Im^B << Py^C < Py^B**.

The reason why **Im^A** and **Py^A** tautomers are much more stable than other is rather obvious. Basic imidazole and pyrazole structures (structures with the lowest energies, i.e. **Im^A** and **Py^A**) are structures in which the cyclic electron delocalization in the ring is possible. So cyclic electron delocalization (aromaticity) has been recognized as a powerful tool for lowering energies of molecular structures. The values of the HOMA index presented in Table 1 show that both studied systems take this opportunity. Pyrazole, as well as imidazole, are highly aromatic compounds. However, the energy of imidazole basic structure (**Im^A**) is lower, despite that the pyrazole structure (**Py^A**) is a bit more aromatic. The introduction of the methylene groups to the rings of other tautomers cut the possibility of cyclic electron delocalization. As results of that, rings of these tautomers lose their flatness and suffer from lack of aromatic stabilization, what significantly increases their energies. The lack of aromaticity is simply reflected in their HOMA values gathered in Table 1, which are around zero or even negative. Really low HOMA values, lower than -0.5 were estimated for the **Py^C** tautomer. In pairs of higher energy-neutral tautomers (**Im^B**- **Im^C** imidazole pair, **Py^B** - **Py^C** pyrazole pair) always the lower HOMA value is predicted for the tautomer with lower energy, i.e. more stable tautomer in the pair. The reason why the **Py^A** system has a bit higher aromaticity than the **Im^A** one results of course from the difference in their molecular structures. It was suggested that aromaticity is lowered if in the ring atoms with different electronegativity are adjacent to each other [32]. In pyrazole, nitrogen atoms with high electronegativity are close together, in imidazole, the carbon separates them. This means that, in the imidazole ring, we have more neighbouring atomic pairs with different electronegativities. This number of pairs of atoms with different electronegativities is reduced for the pyrazole ring.

As we can see, aromaticity is an important energetic factor, but not the only one, and even not the most decisive one. Let's try to consider other effects. In order to do it, let's look at the atomic charges, also gathered in Table 1. In general, nitrogen atoms are negatively charged, while carbon atoms possess a positive partial charge. Charges of hydrogens are around zero, except these from the NH group, where the hydrogen charges are between 0.41 and 0.44. The most important structural change between imidazole and pyrazole is in the relative position of two nitrogen atoms. In imidazole nitrogens are separated by one carbon atom, in pyrazole, they are next to each other. This means, that coulombically stable $N^{q(-)}-C^{q(+)}-N^{q(-)}$ system is replaced by coulombically repulsive $N^{q(-)}-N^{q(-)}$ one. In the imidazole ring, we have four $N^{q(-)}-C^{q(+)}$ atomic pairs, where an atom with a negative charge interact directly with an atom with a positive charge. And one CC pair where both atoms are positively charged.

In contrast, in the pyrazole ring, one pair of strongly negatively charged atoms is observed, and in addition, there are two CC bonds where both atoms have positive charges. Two CN bonds in which one atom has positive and the second negative charge are in the minority in this case. This clearly indicates that the imidazole ring should be more stable than the pyrazole one. This prediction is confirmed, not only by the results from this study, but also by the relative energies calculations of imidazole and pyrazole derivatives with different substituents [12]. For almost all substituents, imidazole derivatives are more stable. The situation changes for Li, Na, BeH, and MgH substituents, was strongly negative nitrogen atoms region of imidazole interact with very strongly positively charged metal atoms.

Let's analyze now energy changes of the same atoms in different tautomer structures of imidazole and pyrazole. Huge differences in relative atomic energies are observed between both nitrogen atoms and carbon atoms C₃ and C₄ in **Im^A** and **Py^A** structures. In comparison to pyrazole, energies of nitrogen atoms are deeply lower and energies of C₃ and C₄ atoms are strongly higher. But, if we add all these huge energy changes for these four atoms they sum is close to zero, -31 kJ/mol and -25 kJ/mol at B3LYP and MP2 levels, respectively. Changes of relative atomic energies for hydrogen atoms are almost balanced too. And quite unexpectedly, decisive is the energy change for the C₅ atom, which is more stable in the **Im^A** structure by about 70 kJ/mol.

Changes in electronic energies among the same atoms in different tautomers of imidazole are relatively small. The same changes in pyrazole tautomers are much higher, see Table 1. The biggest difference between **Im^A** and **Im^B** tautomers is observed for the C₃ atom, the atom where the CH₂ group is created. It is by about 700 kJ/mol more stable in the tautomer with higher energy, i.e. **Im^B**. It is not an easy task to overcome such a large stabilization of the atom C₃.

But on the other hand, there are three atoms in the ring of **Im^B** which are destabilized: N₁ (after transformation from the -NH- group to =N-), and C₄ as well as C₅. Thus there are two main competing mechanisms responsible for relative energy value difference between tautomers **Im^A** and **Im^B**. On one side, attaching of hydrogen to atom C₃ in the **Im^B** structure and formation of the methylene group very strongly decrease the energy of this carbon atom. On the other side energies of other atoms in the ring strongly increase (effect of cyclic electron delocalization destroying, i.e. the disappearance of aromaticity). An exception from that is the N₂ atom, which response is not typical because it is also a proton donor, a hydrogen atom was moved from it to the atom C₃ during the tautomeric transformation from **Im^A** to **Im^B**. Significant impact on the energy difference between tautomers **Im^A** and **Im^B** has also hydrogen H₆. This atom is connected in **Im^A** with the nitrogen atom N₁ and then migrates to the carbon C₃ in the **Im^B** tautomer. This is connected with a significant decrease in its energy as it is well known that hydrogen atoms in OH, NH and NH₂ groups are energetically destabilized [33].

Energetic changes of other atoms are really small. The special case is noticed for nitrogen N₂. B3LYP postulates the lower energy of this atom in tautomer **Im^B**. Opposed prediction is evaluated from the MP2 data. Such a situation is unique and observed only for atom N₂ of the **Im^B** tautomer. Changes in atomic energies between **Im^A** and **Im^C** tautomers are quite similar to those reported between **Im^A** and **Im^B**. However, the methylene group stabilization, which occurs in this case for atom C₅, is about three times lower than it was for atom C₃ in the **Im^B** tautomer. Thus, the **Im^C** tautomer is the structure with the highest energy among imidazole tautomers.

Table 1. Molecular properties of imidazole and pyrazole tautomers.

Structures	Im ^A	Im ^B	Im ^C	Py ^A	Py ^B	Py ^C
Relative free energies (kJ/mol, the energy of the most stable structure is taken as the zero level)						
B3LYP	0.0	72.0	69.6	44.6	158.2	142.8
PBE0	0.0	78.0	74.4	43.7	163.5	149.4
CAM-B3LYP	0.0	75.5	71.9	46.0	164.4	147.0
wB97XD	0.0	75.5	71.7	45.6	163.4	146.7
M06	0.0	73.0	68.6	48.7	165.2	148.2
MP2	0.0	72.2	73.5	43.1	164.3	148.7
CBS-QB3	0.0	69.7	66.9	45.5	156.4	139.4
G4	0.0	67.4	64.5	46.0	152.8	135.5
Aromaticity (HOMA)						
B3LYP/MP2	0.88/0.91	-0.07/0.01	-0.20/-0.16	0.91/0.93	-0.26/-0.13	-0.81/-0.51
Atomic charges (B3LYP/MP2)						
N ₁	-1.17/-1.24	-1.02/-1.02	-1.04/-1.03	-0.74/-0.77	-0.33/-0.33	-0.72/-0.70
N ₂	-1.07/-1.09	-1.02/-1.02	-1.05/-1.07	-0.64/-0.62	-0.37/-0.39	-0.72/-0.70
C ₃	0.94/0.95	0.57/0.57	0.95/0.95	0.48/0.45	0.25/0.26	0.61/0.59
C ₄	0.40/0.41	0.61/0.60	0.62/0.61	-0.03/0.04	-0.05/-0.06	-0.02/-0.06
C ₅	0.32/0.34	0.61/0.60	0.27/0.26	0.38/0.37	0.23/0.22	0.61/0.59
H ₆	0.41/0.43	0.07/0.08	0.06/0.07	0.41/0.44	0.07/0.08	0.06/0.07
H ₇	0.06/0.07	0.07/0.08	0.07/0.07	0.05/0.06	0.06/0.07	0.07/0.08
H ₈	0.05/0.05	0.06/0.06	0.06/0.07	0.04/0.06	0.06/0.07	0.06/0.07
H ₉	0.06/0.07	0.06/0.06	0.06/0.07	0.06/0.07	0.07/0.08	0.07/0.08
Relative atomic energies (kJ/mol, energies of atoms in the most stable Im ^A structure are taken as the zero level, B3LYP/MP2)						
N ₁	0/0	435/636	432/597	591/689	1539/1753	869/1102
N ₂	0/0	-19/31	-68/-59	652/745	993/1045	414/498
C ₃	0/0	-661/-732	-85/-103	-687/-787	-1139/-1201	-550/-644
C ₄	0/0	308/243	292/264	-587/-672	-672/-753	-612/-731
C ₅	0/0	348/282	-177/-257	73,5/61	-272/-361	321/251
H ₆	0/0	-345/-383	-343/-378	3/2	-334/-367	-337/-368
H ₇	0/0	9/6	-3/-6	-15/-12	3/6	6/7
H ₈	0/0	10/7	19/14	10/16	31/36	36/39
H ₉	0/0	-12/-19	7/2	2/1	16/13	2/-2

As it was mentioned earlier, energy changes of the same atoms among pyrazole's are bigger. They are strengthened because if for any reason the negative change of one nitrogen atom increase automatically coulombic repulsion between nitrogens increase and both of these atoms are destabilized. Thus, the main origin of high instability of **Py^B** and **Py^C** tautomers are the high energies of both nitrogen atoms. Nitrogen atoms destabilization is bigger for **Py^C**. Thus, this structure is the least stable among all possible Imidazole and Pyrazole tautomers. These nitrogen atoms destabilization cannot be even balanced by also high stabilizations of carbon atoms. Most of the carbon atoms in **Py^B** and **Py^C** have lower energies than their counterparts in **Py^A** and **Im^A**

structure. Thus **Py^B** and **Py^C** tautomers can be divided into high energy (nitrogens) and low energy part (carbons).

Semi saturated compounds

Adding two hydrogen atoms to the imidazole and pyrazole structures leads to their semi saturated derivatives with only one double bond. As in the case of the imidazole and pyrazole we have again three possible tautomers for each of these main structures. Theoretical structures of all semi saturated tautomers are presented in Fig. 3. In some cases different cis and trans isomers are possible. Always, due to the steric hindrance effects, trans isomers are slightly more stable. Thus only trans isomers are described here.

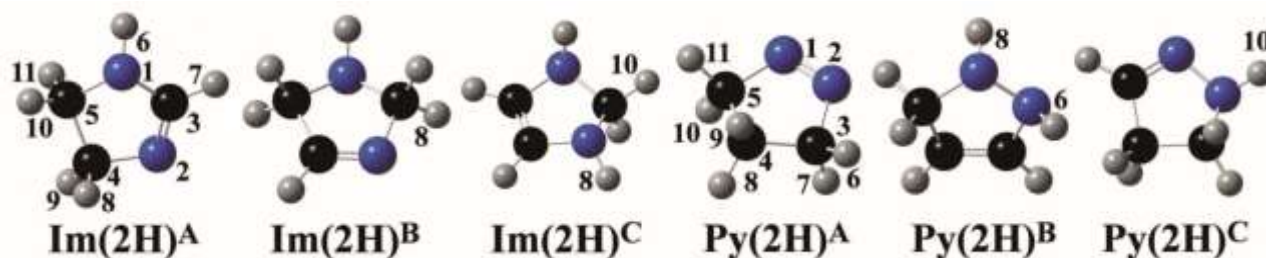


Fig. 3. Optimized structures (MP2/6-311+ +G level) and atom numbering scheme of semi saturated imidazole and pyrazole tautomers (within a particular set of tautomers only numbers of moveable hydrogens are repeated).**

As in the case of unsaturated compounds, the most stable is the structure with the imidazole type of the ring (nitrogen atoms separated by the carbon atom, labelled as **Im(2H)^A**). But here, the similarity ends. The second structure is not a derivative of pyrazole. In the case of semi saturated compounds, each imidazole type structure is more stable than any of the pyrazole ones. Delocalization in the ring is breaking, so aromaticity cannot be considered as a factor (all HOMA values are negative), that can differentiate the stability between both groups (imidazole derivatives and pyrazole derivatives) of studied compounds. In such circumstances, the net of atomic charges is responsible for relative stabilities. As it was mentioned, the ring is only partially unsaturated, so it is difficult to dissipate the negative charges of consecutive nitrogen atoms in pyrazole type tautomers in any way. Because of that, the energy of pyrazole derivatives is significantly higher than in imidazole ones.

Displacement of the H₈ atom from carbon C₄ to carbon C₃ leads to the formation of the structure **Im(2H)^B**, which is about 30-35 kJ/mol less stable than **Im(2H)^A**. The most important reason of that probably is the change of the C₃ atom. The charge of this atom in the **Im(2H)^B** tautomer is about half of the atomic unit less positive. Thus, stabilizing columbic interactions with negatively charged nitrogens is not so effective as for **Im(2H)^A**. Attaching of the second proton to the C₃ atom and formation of the CH₂ group strongly stabilize this atom in the **Im(2H)^B** structure, up to a bit more than 600 kJ/mol. But at the same time, atoms N₁ and C₄ in **Im(2H)^B** strongly increase their energies (in total by more than 800 kJ/mol. Reasons for that are attenuation of columbic interactions between N₁ and C₃, and transformation of the methylene group to the methylylidene one for atom C₄, respectively.

Shifting the proton to the nitrogen N₂, i.e. formation of the **Im(2H)^C** tautomer, also leads to the significant reconfiguration of the relative energies net. Tautomer **Im(2H)^C** has two adjacent methylydene groups located at the C₄ and C₅ atoms. Thus, a bit of delocalization between these two groups is possible. It is of course far away from aromaticity, but even this small amount of delocalization is reflected in the relatively low energies of these carbon atoms. Among effects responsible for the total quite high energy of this structure (total energy of **Im(2H)^C** is about 65 – 70 kJ/mol higher than total energy value for **Im(2H)^A**) are relative energies of nitrogen atoms. In the **Im(2H)^C** structure two NH groups are present and both nitrogen atoms have relatively high energies (on average 220 kJ/mol each). Very important is also very high destabilization of atom H₈ in this tautomer. Common changes of hydrogen atoms energies, which are usually significantly lower than those for

heavy atoms, are from a dozen to several dozen of kJ/mol. However, the displacement of a hydrogen atom from the carbon to the highly negative atom (nitrogen in this case) or in opposite direction is connected with more increase or decrease of its energy.

Let's discuss now relative stability of semi saturated pyrazole derivatives. The most stable among semi saturated tautomers of pyrazole is the tautomer labelled as **Py(2H)^C**. But the stability difference between tautomers **Py(2H)^C** and **Py(2H)^A**, depends on the method of calculations, is small or very small (for example 1.8 kJ/mol for theoretically the most precise G4 method). The relative energy of the **Py(2H)^C** is about 60 kJ/mol higher on average for various calculation methods than powers of **Py(2H)^A** and **Py(2H)^B** and more than 125 kJ higher than **Im(2H)^A**. The **Py(2H)^A** tautomer is clearly divided into two parts, negatively charged and unsaturated (double bond) part of nitrogen atoms and positively charged and fully saturated hydrocarbon part. And on this example, we can observe that when these two parts are separated they manage with that surprisingly-well. The double bond between nitrogen atoms helps them with negative charge delocalization, that's why atomic charges for nitrogen atoms are the less negative ones among all studied structures in this works (i.e. among all known saturated, semi saturated and saturated structures of imidazole and pyrazole). Also hydrocarbon part divide their positive charge in a very smart way. Carbon atoms bounded with nitrogens are positively charged while the charge of the C4 atom, located between this two positively charged carbon atoms, is almost zero. These ways, the net of atomic charges in **Py(2H)^A** is quite well organized, as for atoms connectivity in this structure. In the **Py(2H)^C** tautomer nitrogens charges are significantly more negative, what with no doubt destabilizes this structure. But the situation of the carbons in the hydrocarbons part is mixed, there are two CH₂ and one CH groups. The lower number of hydrogens limits the possibility of unwanted steric interactions. The main problem of the **Py(2H)^B** tautomer is possessing two NH groups. Charges of hydrogens are in these groups very (as for hydrogen, because hydrogen in other groups has a charge close to zero) high positive charge. Thus not only negative nitrogens repulse coulombically but positively charged hydrogens of NH groups repulse each other too.

What's more, the outflow of charge from hydrogen atoms increases the charge on nitrogen and increases their repulsion. These effects are reflected in relative atomic energies between tautomers. For example relative energies of C₃ and C₅ atoms in **Py(2H)^A** (which are located between almost non-charged carbon and negatively charged nitrogens) are low, while energies of hydrogens of NH groups in the **Py(2H)^B** tautomers are pretty high.

Table 2. Molecular properties of semi saturated imidazole and pyrazole tautomers.

Structures	Im(2H) ^A	Im(2H) ^B	Im(2H) ^C	Py(2H) ^A	Py(2H) ^B	Py(2H) ^C
Relative free energies (kJ/mol, the energy of the most stable structure is taken as the zero level)						
B3LYP	0.0	34.9	66.5	76.8	124.9	70.1
PBE0	0.0	35.9	66.2	78.5	125.4	69.9
CAM-B3LYP	0.0	34.2	65.6	81.0	125.4	71.7
wB97XD	0.0	34.8	67.0	79.6	126.9	71.5
M06	0.0	36.0	68.5	85.1	130.8	74.2
MP2	0.0	37.0	71.3	75.5	135.4	72.8
CBS-QB3	0.0	30.9	66.5	73.3	127.7	71.2
G4	0.0	30.5	64.9	71.8	126.1	70.0
Aromaticity (HOMA)						
B3LYP/MP2	-1.27/-1.08	-1.07/-0.83	-0.25/-0.16	-2.42/-2.09	-1.11/-1.01	-1.65/-1.48
Atomic charges (B3LYP/MP2)						
N ₁	-1.05/-1.11	-0.93/-1.01	-0.98/-1.04	-0.31/-0.32	-0.63/-0.66	-0.74/-0.72
N ₂	-1.06/-1.07	-1.06/-1.08	-0.98/-1.04	-0.31/-0.32	-0.70/-0.74	-0.63/-0.68

C ₃	1.04/1.05	0.59/0.63	0.63/0.67	0.24/0.23	0.28/0.29	0.32/0.32
C ₄	0.31/0.31	0.65/0.66	0.28/0.29	0.02/0.01	-0.05/-0.07	0.03/0.01
C ₅	0.32/0.33	0.31/0.33	0.28/0.29	0.24/0.23	0.32/0.33	0.59/0.57
H ₆	0.36/0.38	0.33/0.35	0.34/0.36	0.03/0.03	0.35/0.37	-0.01/-0.01
H ₇	0.05/0.06	0.02/0.01	-0.03/-0.03	0.03/0.03	0.05/0.06	0.02/0.02
H ₈	0.01/0.02	0.02/0.02	0.34/0.36	0.00/0.01	0.34/0.35	0.01/0.02
H ₉	0.01/0.02	0.04/0.05	0.04/0.06	0.01/0.02	0.03/0.05	0.01/0.02
H ₁₀	-0.01/0.00	0.01/0.00	0.02/0.03	0.03/0.03	0.00/0.00	0.36/0.38
H ₁₁	0.01/0.01	0.02/0.01	0.04/0.06	0.03/0.03	0.00/0.01	0.05/0.06

Relative atomic energies (kJ/mol, energies of atoms in the most stable Im(2H)^A structure are taken as the zero level, B3LYP/MP2)

N ₁	0/0	376/359	231/235	1077/1240	853/929	383/559
N ₂	0/0	-99/-100	212/114	1057/1120	599/575	655/618
C ₃	0/0	-609/-625	-474/-515	-1137/-1269	-1107/-1173	-946/-1054
C ₄	0/0	444/493	-92/-31	-382/-435	-542/-560	-392/-429
C ₅	0/0	-63/-33	-144/-99	-224/-252	-11/-6	351/346
H ₆	0/0	-65/-49	-36/-34	-343/-368	-32/-30	-362/-384
H ₇	0/0	-52/-72	-91/-99	-33/-34	4/10	-72/-76
H ₈	0/0	6/-4	332/358	6/17	300/323	13/17
H ₉	0/0	52/49	59/66	-7/-7	56/66	18/23
H ₁₀	0/0	14/-5	-7/-10	26/22	-9/-15	349/370
H ₁₁	0/0	31/27	77/90	43/47	13/19	75/85

Fully saturated compounds

Saturation of the second double bond in the imidazole and pyrazole structures results in lacking of tautomeric structures. Only one structure is possible for saturated imidazole and one for saturated pyrazole. Calculated geometries of the above-mentioned structures are presented in Fig. 4.

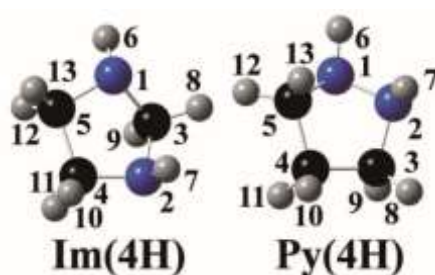


Fig. 4. Optimized geometries (MP2/6-311++G level) and atom numbering scheme of fully saturated imidazole and pyrazole structures.**

The total lack of π electron delocalization possibility should even increase in the relative importance of charge distribution. All theoretical approaches involved in calculations are very consistent. The energy of fully saturated imidazole derivative is lower by about 70 kJ than the energy of fully saturated pyrazole (the energy gap between these two compounds is between 67.7 for PBE0 functional and 70.6 kJ/mol for the MP2 ab initio perturbation method). With no doubts, the origin of the pyrazole-like system lower stability can be attributed to the high concentration of negative charge in the NN unit. Both nitrogen atoms in the **Im(4H)** compound are more

negative than these atoms in **Py(4H)** (about -1 for **Im(4H)** and -0.65 for **Py(4H)**). But highly negative nitrogen atoms in **Im(4H)** are separated by positively charged (charge about 0.65) C₃ atom. Such an alternate set of positive and negative charges stabilizes **Im(4H)**. In the case of **Py(4H)** negative charge of nitrogen atom is not so big (two nitrogen atoms, with the same electronegativity, are able to diminish a bit negative partial charges on nitrogens), but in case of **Py(4H)** these two still powerfully negatively charged atoms are not separated by any buffer. Significant changes of relative energies between atomic pairs in **Im(4H)** and **Py(4H)** are observed only between nitrogen atoms and carbon atoms C₃ and C₄. The situation of atom C₅ does not vary much between **Im(4H)** to **Py(4H)**, so the energy difference for this atom also is not very big. Nitrogen atoms in the **Py(4H)** structure are energetically destabilized by more than 400 kJ (and even more than 500 kJ as for N₂ at the MP2 level). In the contrary, all carbon atoms are more stable in the **Im(4H)** structure. These energy differences are a bit smaller than for nitrogen atoms and almost the same for both carbon atoms. This is not very surprising, because after transformation from **Im(4H)** to **Py(4H)** changes in these atoms environment are similar.

Table 3. Molecular properties of fully saturated imidazole and pyrazole tautomers.

Structures	Im(4H)	Py(4H)
Relative free energies (kJ/mol, the energy of the most stable structure is taken as the zero level)		
B3LYP	0.0	68.0
PBE0	0.0	67.7
CAM-B3LYP	0.0	70.2
wB97XD	0.0	69.6
M06	0.0	70.1
MP2	0.0	70.6
CBS-QB3	0.0	68.3
G4	0.0	68.9
Aromaticity (HOMA)		
B3LYP/MP2	-1.93/-1.84	-3.00/-2.82
Atomic charges (B3LYP/MP2)		
N ₁	-0.96/-1.01	-0.65/-0.68
N ₂	-0.94/-0.99	-0.62/-0.65
C ₃	0.63/0.66	0.33/0.34
C ₄	0.33/0.33	0.03/0.01
C ₅	0.32/0.32	0.31/0.32
H ₆	0.32/0.35	0.34/0.35
H ₇	0.33/0.34	0.28/0.30
H ₈	0.01/0.02	0.01/0.02
H ₉	-0.01/-0.01	0.00/0.01
H ₁₀ , H ₁₁	0.00/0.01	0.00/0.00
H ₁₂ , H ₁₃	-0.04/-0.01	-0.01/0.01
Relative atomic energies (kJ/mol energies of atoms in the more stable Im(4H) are taken as the zero level, B3LYP/MP2)		
N ₁	0/0	407/476
N ₂	0/0	480/528
C ₃	0/0	-404/-455

C ₄	0/0	-406/-463
C ₅	0/0	-32/-38
H ₆	0/0	12/8
H ₇	0/0	-40/-45
H ₈	0/0	24/30
H ₉	0/0	-2/-3
H ₁₀	0/0	11/16
H ₁₁	0/0	-6/-2
H ₁₂	0/0	-14/-25
H ₁₃	0/0	35/44

Conclusions

Calculations for 14 different structures of imidazole and pyrazole as well as their semi and fully saturated derivatives (three unsaturated tautomers, three semi saturated tautomers, and one fully saturated structure for imidazole and the same for pyrazole) have been performed. Calculations supported that the most stable structures for native pyrazole and imidazole are so-called "aromatic" tautomers, in which full electron delocalization in the ring is possible. The most stable tautomers of semi saturated pyrazole and imidazole have been determined. In both cases, the most stable structures of semi saturated compounds consist of two (adjacent CH₂ groups, one CH, one NH and one nitrogen atom without any hydrogen connected with it. Of course, the sequence of these building blocks is different but it looks that this set is optimal. Only one structure is possible for fully saturated derivatives. In general imidazole and their derivatives are more stable than pyrazole and its derivatives. In each group of studied compounds (tautomers of unsaturated native imidazole and pyrazole, tautomers of their semi saturated derivatives and fully saturated derivatives) the structure containing the imidazole ring is more stable. Aromaticity is an important energetic factor of native imidazole and pyrazole stabilization. Thanks to that, two of the lowest structures of unsaturated compounds are the structures in which efficient aromaticity is possible. But not aromaticity is a decisive force. The aromaticity of the most stable tautomer of native pyrazole has a bit higher aromaticity than its imidazole counterpart. But the imidazole structure is more stable. The most important factor for the relatively high stability of structures with imidazole ring is the high concentration of negative charge in the NN group of pyrazole and all consequences of this. The characteristic NCN moiety of imidazole, in which two highly negative nitrogen atoms are separated by the positively charged carbon atom is much more stable and is responsible for higher stability of the imidazole ring.

Data Availability (excluding Review articles)

Some raw data are available as Supplementary Materials to this article.

Conflicts of Interest

The author declares no conflict of interest.

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There is no specific funding statement.

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Supplementary Materials

Coordinates of the studied compounds minima calculated at the B3LYP/6-311++G** and MP2/6-311++G** computational levels are available as supplementary data to this paper.

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Supplementary Materials**Coordinates of the studied compounds minima calculated at the B3LYP/6-311++G** computational level.**Im^A

C 0.62642000 0.97461000 0.00010200
H 1.09442100 1.94452800 0.00020000
C 1.13298200 -0.29894400 -0.00011500
H 2.16827800 -0.60166600 -0.00015200
H -1.42985200 1.55507900 0.00023300
N -0.74439600 0.81657700 -0.00012600
C -0.99659000 -0.52683000 -0.00002600
N 0.11428400 -1.22561800 0.00011500
H -1.99893800 -0.92767100 0.00003000

Im^B

N 0.00000000 1.18968600 0.29322700
N 0.00000000 -1.18968600 0.29322700
C 0.00000000 0.00000000 1.13162900
H -0.88108800 0.00000000 1.78372000
H 0.88108800 0.00000000 1.78372000
C 0.00000000 0.73908800 -0.90878700
C 0.00000000 -0.73908800 -0.90878700
H 0.00000000 1.38718400 -1.77847200
H 0.00000000 -1.38718400 -1.77847200

Im^C

N 1.19608400 0.35538600 0.00000000
N -1.11460400 0.50655100 0.00000000
C 0.76626200 -0.85661600 0.00000000
H 1.43578900 -1.71028400 0.00000000

C 0.00000000 1.13787400 0.00000000
C -0.73280400 -0.90083900 0.00000000
H -1.14197600 -1.41210700 0.87981200
H -1.14197600 -1.41210700 -0.87981200
H 0.07705400 2.21842400 0.00000000
Py^A
C 0.71339700 0.90588500 -0.00006400
H 1.48566500 1.65827300 -0.00019300
C -0.66313000 0.99855800 0.00007500
H -1.25624700 1.89805700 0.00003500
C -1.11045900 -0.34229100 -0.00005100
H -2.12413500 -0.71376300 -0.00019400
N -0.09599200 -1.20201100 0.00000500
H 1.91061400 -0.85599300 -0.00044000
N 1.00245800 -0.42077200 0.00014200
Py^B
C -1.15896900 0.22924800 0.00000000
H -2.20240400 0.50491900 0.00000000
C -0.62614600 -0.99917700 0.00000000
H -1.09710000 -1.97056100 0.00000000
N 0.80517200 -0.92166900 0.00000000
N 1.18011100 0.27749300 0.00000000
C 0.00000000 1.16147800 0.00000000
H 0.05660600 1.81279100 0.88042600
H 0.05660600 1.81279100 -0.88042600
Py^C
C 0.00000000 1.12736400 0.20499800

H 0.00000000 2.18465400 0.44262000

C 0.00000000 -1.12736400 0.20499800

H 0.00000000 -2.18465400 0.44262000

N 0.00000000 -0.72372500 -1.01132400

N 0.00000000 0.72372500 -1.01132400

C 0.00000000 0.00000000 1.18840300

H -0.88095500 0.00000000 1.84145200

H 0.88095500 0.00000000 1.84145200

Im(2H)^A

H -1.23069400 1.70915200 0.21504100

N -0.67806600 0.95517000 -0.16805300

C -1.12195100 -0.34868100 0.02021800

N -0.23904900 -1.26745600 0.07851400

H -2.18918800 -0.54385100 0.06583300

C 0.77212100 0.92827400 0.09908200

H 1.31892200 1.55678300 -0.60512900

H 0.99170300 1.26770100 1.11927600

C 1.06475600 -0.58549500 -0.07581800

H 1.78613200 -0.96744100 0.64842900

H 1.45337000 -0.80092500 -1.07757100

Im(2H)^B

H 0.24649300 1.58867600 0.97074300

N 0.18269900 1.19392200 0.03994700

N 0.51679100 -1.17219900 0.07564600

C -1.11290800 0.50972400 -0.11030300

H -1.85180600 0.85795800 0.61655800

H -1.54071200 0.66919400 -1.11003000

C -0.73298900 -0.95004400 0.06588700

C 1.19128800 0.12692200 -0.10875100

H 2.00811000 0.24423400 0.60665800

H 1.62406300 0.12845800 -1.11640900

H -1.45491700 -1.76019300 0.14233000

Im(2H)^C

C -0.90630800 -0.79914700 -0.01228800

C -1.10605100 0.52029200 -0.08216900

H -2.03519700 1.06047000 -0.16890000

H -1.63608400 -1.59301600 -0.05815700

C 1.15628400 0.16626200 -0.14838200

H 1.46167800 0.13193200 -1.20608500

H 2.03403400 0.35220600 0.47155600

N 0.14715500 1.22357000 0.01842800

H 0.23827500 1.68195200 0.92201900

N 0.46158300 -1.08810600 0.23109700

H 0.81258000 -1.90623900 -0.25007000

Py(2H)^A

N 0.04373700 -1.11246400 0.61640800

C 0.04373700 0.26683300 1.19179000

H -0.73046800 0.31180600 1.95980800

H 1.00892700 0.39610600 1.69151000

C -0.17262100 1.21403000 0.00000000

H 0.52633000 2.05018500 0.00000000

H -1.18468500 1.62231200 0.00000000

N 0.04373700 -1.11246400 -0.61640800

C 0.04373700 0.26683300 -1.19179000

H 1.00892700 0.39610600 -1.69151000

H -0.73046800 0.31180600 -1.95980800

Py(2H)^B

C -1.22808800 0.11157100 -0.11539600

H -1.71261700 0.15896800 -1.10128700

H -2.02262500 0.11935700 0.63654200

H -0.56657500 -1.50473900 0.95835900

H 1.42277700 -1.12098400 -0.82713200

N -0.42003300 -1.13225900 0.02656600

N 0.98210800 -0.74167000 0.00738400

C -0.20945300 1.21813000 0.05402100

C 1.00697600 0.67405600 0.04420000

H -0.43958500 2.27107900 0.12142000

H 1.96748700 1.17127700 0.07749700

Py(2H)^C

C 1.18775500 -0.20127800 0.07967500

H 2.25452400 -0.35604700 0.17977800

N 0.39222600 -1.20152600 0.03296000

H -1.57645000 -1.33487700 0.24709900

N -0.90161300 -0.73629300 -0.21121400

C -0.96224100 0.70048200 0.13860900

H -1.68590600 1.22091800 -0.48881800

H -1.23361900 0.84474300 1.19412300

C 0.49473300 1.13180900 -0.10661100

H 0.84261400 1.90789500 0.57698800

H 0.64306400 1.49602300 -1.13143200

Im(4H)

H 0.61374100 2.02523400 -0.14039500
N 0.37181600 1.13334000 0.27770000
C -1.02358500 0.74516800 -0.00974400
H -1.68167600 1.08019500 0.79652100
H -1.40097700 1.16962700 -0.95028200
C -0.94985200 -0.80948500 -0.11425100
H -1.23964300 -1.13849000 -1.11589500
H -1.60006700 -1.31480100 0.60109300
N 0.45969600 -1.17655200 0.12897300
H 0.58820000 -1.34595100 1.12164200
C 1.20305900 0.02305000 -0.22325900
H 1.33137800 0.04767000 -1.31818100
H 2.19073400 0.02660600 0.24232000
Py(4H)
H 1.65533500 -1.33424400 -0.10668400
N 0.90191700 -0.70785500 -0.36780700
C -0.39231000 1.21285500 -0.00317200
H -0.49152700 1.82904500 -0.89853200
H -0.67777800 1.82146000 0.85716100
C 1.04482800 0.66464900 0.14620500
H 1.35404000 0.68649400 1.20485500
H 1.78142800 1.21680800 -0.44084900
C -1.24969300 -0.08616400 -0.12254400
H -1.62255500 -0.20703800 -1.14103900
H -2.09754900 -0.11207100 0.56400200
N -0.33937200 -1.20524200 0.17380100
H -0.25615800 -1.25681800 1.19619100

Coordinates of the studied compounds minima calculated at the MP2/6-311+ +G computational level.**Im^A

C 0.53265400 1.03271000 -0.00008600
H 0.91101600 2.04349300 -0.00013600
C 1.15638500 -0.20071300 0.00008700
H 2.21742300 -0.40518700 0.00015700
H -1.56600900 1.42313700 0.00004900
N -0.81397100 0.74913500 0.00004600
C -0.94849400 -0.61172100 0.00005500
N 0.22936400 -1.21843300 -0.00008600
H -1.91344400 -1.09801900 -0.00012400

Im^B

N 0.00000000 1.19773200 0.30044800
N 0.00000000 -1.19773200 0.30044800
C 0.00000000 0.00000000 1.13000000
H -0.88778700 0.00000000 1.77263200
H 0.88778700 0.00000000 1.77263200
C 0.00000000 0.73678900 -0.91391600
C 0.00000000 -0.73678900 -0.91391600
H 0.00000000 1.38832400 -1.78227600
H 0.00000000 -1.38832400 -1.78227600

Im^C

N 1.20394300 0.36251500 0.00000000
N -1.12518800 0.50202600 0.00000000
C 0.76626600 -0.85869800 0.00000000
H 1.43748000 -1.71226500 0.00000000
C 0.00000000 1.13833000 0.00000000

C -0.73121300 -0.90360400 0.00000000

H -1.13555300 -1.40795000 0.88595500

H -1.13555300 -1.40795000 -0.88595500

H 0.07202300 2.22021700 0.00000000

Py^A

C 0.66808700 0.94636600 0.00000700

H 1.40707900 1.73435200 -0.00010200

C -0.72111600 0.96324500 0.00000400

H -1.36065400 1.83311300 -0.00010500

C -1.09644500 -0.39620100 0.00003100

H -2.08726700 -0.82867200 -0.00009300

N -0.02370400 -1.21214600 -0.00003400

H 1.95424800 -0.75450100 -0.00031800

N 1.02133800 -0.36853300 0.00008600

Py^B

C -1.16198400 0.23561000 0.00000000

H -2.20820500 0.50862300 0.00000000

C -0.62453100 -1.00314100 0.00000000

H -1.10036300 -1.97452300 0.00000000

N 0.80376100 -0.93230600 0.00000000

N 1.18344600 0.28667800 0.00000000

C 0.00000000 1.16299600 0.00000000

H 0.05860600 1.80625400 0.88649900

H 0.05860600 1.80625400 -0.88649900

Py^C

C 0.00000000 1.12581800 0.21246600

H 0.00000000 2.18565800 0.44358000

C 0.00000000 -1.12581800 0.21246600
H 0.00000000 -2.18565800 0.44358000
N 0.00000000 -0.72234100 -1.02012300
N 0.00000000 0.72234100 -1.02012300
C 0.00000000 0.00000000 1.19438200
H -0.88720000 0.00000000 1.83933900
H 0.88720000 0.00000000 1.83933900
Im(2H)^A
H -1.29587200 1.64940000 0.19438100
N -0.70780400 0.92765300 -0.20392600
C -1.10235200 -0.39071500 0.02708400
N -0.17581600 -1.28118900 0.10316600
H -2.16191900 -0.62841700 0.08040300
C 0.72396500 0.94907900 0.13732900
H 1.27699400 1.63881500 -0.50239500
H 0.87439100 1.22057500 1.19107700
C 1.08250600 -0.52953300 -0.10837900
H 1.86855200 -0.89695000 0.55334200
H 1.39847900 -0.68166200 -1.14768700
Im(2H)^B
H 0.20668200 1.98255700 0.37217700
N 0.11003900 1.15546300 -0.20548000
N 0.58696000 -1.14697400 -0.02050500
C -1.14949500 0.45096300 0.05757200
H -1.58124100 0.64311500 1.05411700
H -1.91262700 0.68350300 -0.69287200
C -0.68490100 -0.98238300 -0.02236600

C 1.19158600 0.18341800 0.05518900
H 1.64605200 0.28781500 1.05227200
H 1.98029000 0.26638300 -0.69728900
H -1.36129100 -1.83477900 -0.04887900
Im(2H)^C
C -0.80845100 -0.89214300 -0.01917800
C -1.14883500 0.40970300 -0.09236800
H -2.13154300 0.84785700 -0.19171700
H -1.45100800 -1.76098500 -0.07448600
C 1.11316100 0.28360900 -0.18306600
H 1.32059400 0.26546000 -1.26448200
H 2.01178000 0.56198500 0.36940800
N 0.02537400 1.23698400 0.05019400
H 0.07980800 1.59635100 1.00344600
N 0.57763900 -1.02418500 0.25609100
H 1.01402100 -1.80727500 -0.21849500
Py(2H)^A
N 0.06313000 -1.10322600 0.61442100
C 0.06313000 0.27277300 1.17665700
H -0.65152500 0.31204600 2.00198300
H 1.06174700 0.42984900 1.60317900
C -0.25036100 1.18578600 0.00000000
H 0.34601600 2.09965500 0.00000000
H -1.30568100 1.47373000 0.00000000
N 0.06313000 -1.10322600 -0.61442100
C 0.06313000 0.27277300 -1.17665700
H 1.06174700 0.42984900 -1.60317900

H -0.65152500 0.31204600 -2.00198300

Py(2H)^B

C -1.22096800 0.11124700 -0.13671200

H -1.64447600 0.14583700 -1.15003200

H -2.04937300 0.12425900 0.57747800

H -0.55116200 -1.41946600 1.02499100

H 1.35963900 -1.10731100 -0.88361300

N -0.42552700 -1.12601600 0.06038700

N 0.97450100 -0.75439200 -0.00980600

C -0.20982100 1.21982900 0.06617600

C 1.01327700 0.66660400 0.04532700

H -0.43150900 2.27642600 0.14120000

H 1.97913300 1.15703300 0.08716100

Py(2H)^C

C 1.12169800 -0.42766100 0.09494000

H 2.13269600 -0.80135300 0.21028700

N 0.13242300 -1.25960000 0.03910300

H -1.81554700 -0.97264400 0.21745200

N -1.02865200 -0.52503900 -0.23991500

C -0.78750000 0.87102600 0.17358900

H -1.42311200 1.55464800 -0.39083900

H -0.95874900 1.00183500 1.25304600

C 0.70646500 1.00720800 -0.13502600

H 1.22424400 1.72714200 0.50129700

H 0.87009200 1.27939500 -1.18657100

Im(4H)

H -0.81986400 1.95326300 0.05787500

N -0.47943700 1.07327400 -0.32175200

C 0.92848900 0.84293800 0.04471000

H 1.59298600 1.28946700 -0.69952400

H 1.18138100 1.25684000 1.03175500

C 1.02616800 -0.71100700 0.08572100

H 1.38937600 -1.04555200 1.06135900

H 1.69326400 -1.11046700 -0.68120500

N -0.34582400 -1.21846200 -0.12140900

H -0.47789800 -1.36611300 -1.11871700

C -1.18053400 -0.08702000 0.24751200

H -1.23989200 -0.04647500 1.34799200

H -2.18726100 -0.18410800 -0.16506600

Py(4H)

H 1.72425700 -1.22595100 -0.12347300

N 0.93170100 -0.64652500 -0.38776400

C -0.45881900 1.18624900 -0.01716600

H -0.56954800 1.76820900 -0.93496400

H -0.78964900 1.80027300 0.82411200

C 0.99648000 0.71522100 0.16326100

H 1.26373400 0.71204500 1.23351700

H 1.72166000 1.31956600 -0.38666900

C -1.23814100 -0.15828600 -0.11525400

H -1.60961900 -0.31421700 -1.12997700

H -2.07320200 -0.22718600 0.58587300

N -0.26150700 -1.21931500 0.17975400

H -0.15610700 -1.23096600 1.20261100