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Protonation Sites in Benzimidazolyl-Chalcones Molecules: An *ab Initio* and DFT Investigation

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Abstract

In this work, we have focused our investigations on the protonation sites predilection in the benzimidazolyl-chalcones (BZC) derivatives. Particularly, we are interested in the study of geometrical and energetical parameters. BZC are well known for their particularly nematicidal activity. Ten (10) BZC derivatives coded BZC-1 to BZC-10, with various larvicidal concentrations, have been selected for this work. They all are different one from another by the phenyl ring which is substituted by electron modulators such as alkyl, hydroxyl, alkoxy, aminoalkyl, halogen and nitro or replaced by the furan. Quantum chemical methods, namely HF/6-311 + G(d,p) and MPW1PW91/6-311 + G(d,p) theory levels have been used to determine the geometrical and energetical parameters by the protonation on each heteroatom of the BZC derivative. An accuracy results with relatively less time consuming has been obtained using Hartree-Fock (HF) and Density Functional Theory methods (DFT/MPW1PW91). The calculations results allow identifying the sp^2 nitrogen as the preferential site of protonation in BZC derivative compounds.

Keywords

Benzimidazolyl-Chalcone, Quantum Chemistry, Protonation, Proton Affinity, Gas Phase Basicity

1. Introduction

The derivatives of the benzimidazolyl present a pharmacological interest significantly due to their therapeutic

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virtues in many diseases. Several studies have demonstrated that the derivatives of benzimidazolyl are antihistaminic [1], antifungal [2], antiallergic [3], antibacterial [4]-[6], analgesic [7], antiplasmodial [8] and antiviral [9]. In recent years, it has been documented and reported that the main cause of gastro-intestinal infections of small ruminants as well as loss and reduction in productivity of the livestock is due to the effect of nematodes [10] [11]. Nematodes (worm from hearth, freshwater or sea) are also being the origin of most human parasitic diseases [12] [13]. The development of an "ideal" anthelmintic seems to be possible with the benzimidazoles, imidazothiazoles, tetrahydropyrimidines and organophosphate compounds. Such ananthelmintic should possess a broad spectrum of action, a high degree of efficiency, a good safety margin and aflexibility of use. However, all reported studies related to benzimidazolyl-chalcones are limited to the synthesis, structural characterization and the investigation of the activity properties. Till date, researches have led to synthesize several hundred of compound. A few have been selected for their effective anthelmintic activity at broad spectrum, and among them, the benzimidazolyl-chalcones (BZC) kernel.

These different molecules have been synthesized by Ouattara *et al*. [14]. The numerous therapeutic properties of BZC could be related to the conformation of molecules and the interactions they can establish with other molecules. Among the different properties of a biological molecule, the proton-transfer reactions play a very important role in the molecular interactionsand biologicalsystems [15] [16]. The BZC ability to protonate is likely to affect its fate in the environment, both as regards its transport, his stay, its reactivity in the surrounding environment until the target molecule and as regards its recognition by the receiver. Protonation or deprotonation is the first step in many fundamental chemical rearrangements and in most of the enzymatic reactions [16]. Two quantities are used to characterize the ability of a molecule in the gas phase or phase condensed to accept a proton. The gas phase basicity (*GB*) which is the opposite of the variation of free energy associated with the protonation reaction ($GB = -\Delta G^0_{298}$) and the proton affinity ($PA = -\Delta H^0_{298}$) [17]-[19]. The gas phase basicity and the proton affinity (*PA*) can inform us on the capacity of a site to accept a proton. A recently work [20] has tried to determine the preferential site of protonation between nitrogen atoms and oxygen. The aim of our present work is to characterize the preferential site of protonation in benzimidazolyl-chalcones by using different quantum chemical methods.

2. Computational Details

2.1. The Calculation Level

All the calculations have been carried out, on ten BZC compounds (**Figure 1**), with the software GAUSSIAN 03 [21], in vacuo, at the HF/6-311 + G(d,p) and MPW1PW91/6-311 + G(d,p) theories levels. Choosing Hartree-Fock (HF) and Density Functional Theory methods (DFT/MPW1PW91) allows accuracy results with relatively

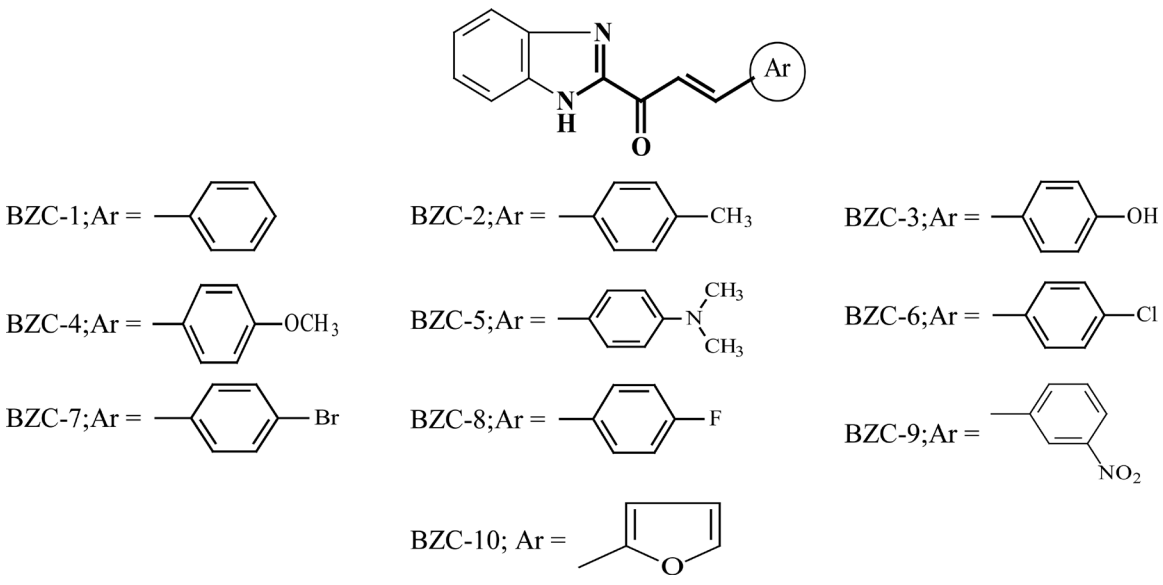

Figure 1. Structure of the benzimidazolyl-chalcones (BZC) studied.

less time consuming. Usually, it's highly recommended to use at least two different methods in quantum mechanical calcultions, so that consistency of results can be, in some way, verified. The choice of split-valence and triple-dzeta basis sets is justified by the need of sufficiently extended levels. Diffuse and polarization functions are important, whenever the matter is intermolecular interactions. Each of the protonation complexes has been fully optimized, with a frequencies calculation at the same levels of theories.

2.2. Geometry Optimization

Geometry initialization of the protonated molecules has been carried out by utilizing the valence angles around the concerned heteroatoms (carbonyl oxygen, sp^2 and sp^3 nitrogens) of the benzimidazolyl-chalcones (BZC) kernel. According to Gillespie method or V.S.E.P.R (Valence Schell Electron Pair Repulsion) method, the average values of valence angles around sp^2 and sp^3 atoms equal $\tau_m = 120^\circ$ and $\tau_m = 109.5^\circ$ respectively. **Figure 2** shows the initial geometries of protonation.

2.3. Energetic Parameters

The protonation is a process in which a Lewis base B fixed a proton to give a protonated molecule BH^+ according Equation (1):

$$B + H^+ \rightleftarrows BH^+ \tag{1}$$

Knowing the variations of energy contributions to the internal energy at 0 K and at 298.15 K between the products and reactants contributes to the energy characterization of a chemical reaction. For a given energy parameter *X*, its variation is determined according Equation (2):

$$\Delta X = \sum X(\text{products}) - \sum X(\text{reactants}) \tag{2}$$

The geometrical optimization and the calculation of the frequencies of the free molecules allow us to determine the variation of the internal energy at 0 K (ΔE_{0K}) and at 298.15 K (ΔE_{298K}) with respect to the reaction studied. The variation of the internal energy to 298.15 K, ΔE_{298K}, constitutes a sum of different electronic, translation, rotation and vibration contributions and the internal energy at 0 K given in Equation (3):

$$\Delta E_{298K} = \Delta E_{el} + \Delta E_{trans} + \Delta E_{rot} + \Delta E_{vib,therm} + \Delta E_{0K} \tag{3}$$

ZPVE (Zero Point Vibrational Energy) contribution, *i.e.* lowest vibrational level energy, due to 3N − 6 normal vibrational modes (3N − 5 for the linear molecules), each with frequency ν_i, up to N kernels at 0 K, is defined according Equation (4):

$$\text{ZPVE} = \frac{1}{2} R \sum_{i=1}^{3N-6} \left(\frac{h_i}{k} \right) \tag{4}$$

k is the Boltzmann constant; *h* Planck's constant; *R* the constant of perfect gases. To obtain the corresponding energy at 298.15 K, it is necessary to take into account the extra energy due to vibrational levels population during temperature rising from 0 to 298.15 K. Thus, Equation (4) becomes Equation (5):

$$E_{vib,therm} = R \sum_{i=1}^{3N-6} \frac{h_i / k}{e^{(h_i / T(K))} - 1} \tag{5}$$

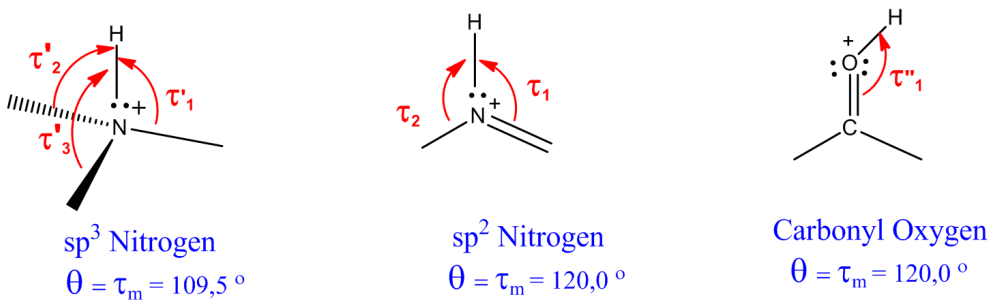

Figure 2. Definition of geometrical parameters describing the protonation sites.

As regards the contributions of rotation and translation, they are drawn from the approximation of perfect gases according relationship (6):

$$\Delta E_{\text{trans}} = \Delta E_{\text{rot}} = -\frac{3}{2}RT \tag{6}$$

As a result, internal energy variation at 298.15 K is given by Equation (7):

$$\Delta E_{298\text{K}} = \Delta E_{\text{el}} + \Delta\text{ZPVE} + \Delta E_{\text{vib,therm}} - 3RT \tag{7}$$

From this relationship, it is deducted the enthalpy of the reaction at 298.15 K. It corresponds to the variation of the internal energy corrected by the term Δ(PV), either ΔnRT (Δn being the variation in the number of gaseous moles of the reaction):

$$\Delta H_{298\text{K}} = \Delta E_{298\text{K}} + \Delta nRT \tag{8}$$

The entropic contributions of translation S_{trans}, of rotation S_{rot} and of vibration S_{vib} of given species at 298.15 K are regrouped in the total entropy term *S* and the Gibbs energy, at 298.15 K, linked to the reaction is simply obtained by the relationship (9):

$$\Delta G_{298\text{K}} = \Delta H_{298\text{K}} - T\Delta S_{298\text{K}} \tag{9}$$

The electronic energy of an isolated proton equals zero, therefore it doesn't appear in the calculation of the variation of the electronic energy. Again, for the proton, the translational energy is different from zero ($E\left(\text{H}^+\right)_{298\text{K}} = 3/2\,RT = 0.889$ kcal/mol·K at 298.15 K and the entropy of translation equals $S\left(\text{H}^+\right) = 26.027$ kcal/mol·K. Therefore, the proton affinity in the gas phase (PA) and the gas phase basicity (GB), are easily determined according the above equations.

3. Results and Discussion

3.1. Geometrical Parameters

The descriptors selected for this study are related to the average valence angles around the potential protonated sites N_{sp2}, O_{sp2} and N_{sp3}. It is assumed that in sp^2 hybridization state, each of the lone pairs of the oxygen atom forms with the carbonyl bond C=O an angle of 120.0˚, and that the lone pair of the nitrogen atom also points out with an angle of 120.0˚ with each adjacent bond. In the case of sp^3 nitrogen, the optimal angle is assumed to be 109.5˚. It is clear from these observations that the binding geometry, the more probable, which can be formed between hydrogen and each basic site, will be the one measuring the average valence angles θ_m, which better approaches the optimal angles. The values measured of the valence angles θ_m are shown in **Table 1**. In this table, $\theta_1\text{Nsp}^2$ equals the average of the angles τ_1 and τ_2, when $\theta_3\text{Nsp}^3$ equals the average of the angles

Table 1. Average angles of protonated BZC on the sp^2($\theta_1\text{Nsp}^2$), sp^3 ($\theta_3\text{Nsp}^3$) nitrogenatoms and carbonyl oxygen ($\theta_2\text{Osp}^2$) calculated at the HF/6-311 + G(d,p) and MPW1PW91/6-311 + G(d,p) levels (Values expressed in ˚).

	HF/6-311 + G(d,p)			MPW1PW91/6-311 + G(d,p)		
	$\theta_1\text{Nsp}^2$	$\theta_2\text{Osp}^2$	$\theta_3\text{Nsp}^3$	$\theta_1\text{Nsp}^2$	$\theta_2\text{Osp}^2$	$\theta_3\text{Nsp}^3$
BZC-1	125.39	115.28	110.14	125.13	112.86	110.02
BZC-2	125.39	115.22	109.50	125.13	112.79	110.01
BZC-3	125.39	115.22	110.12	125.13	112.75	109.99
BZC-4	125.39	115.14	110.10	125.13	112.69	109.98
BZC-5	125.37	114.70	110.07	125.13	112.36	109.91
BZC-6	125.40	115.34	110.15	125.13	112.90	110.03
BZC-7	125.40	115.33	110.15	125.14	112.88	110.02
BZC-8	125.39	115.35	110.14	125.13	112.95	110.02
BZC-9	125.40	115.56	110.16	125.14	113.18	110.06
BZC-10	125.40	115.30	110.14	125.14	113.09	110.01

τ_1', τ_2' and τ_3'. $\theta_2 Osp^2$ stands for τ_1'' describing the angle $C=O^+\text{-}H$ (**Figure 2**).

The review of the values in **Table 1** shows that respectively at HF/6-311+G (d,p) and MPW1PW91/6-311 + G(d,p) levels, the average values of the angles extend for $\theta_1 Nsp^2$, from 125.37˚ to 125.40˚ and from 125.13˚ to 125.14˚; for $\theta_2 Osp^2$, from 114.70˚ to 115.56˚ and from 112.36˚ to 113.18˚ and for $\theta_3 Nsp^3$, from 109.50˚ to 110.16˚ and from 109.91˚ to 110.06˚ respectivelyat the HF/6-311 + G(d,p) and MPW1PW91/6-311 + G(d,p) levels. Now, let's examine which calculated angles are closer to the theoretical optimal angles according to **Figure 2**. For bothlevels of theories, the average $\theta_1 Nsp^2$ angles vary from 125.13˚ to 125.40˚ corresponding to a maximum gap of 5.40˚comparing with the ideal angle of 120.0˚. Samely, the maximum gaps obtained for $\theta_2 Osp^2$ and $\theta_3 Nsp^3$ are respectively 7.64˚ and 0.66˚. And finally, the form $N_{sp3}\text{-}H^+$ corresponding to the angle $\theta_3 Nsp^3$, shows theclosestvalue to the theoretical one. Which confirms the tetragonalisation of sp^3 nitrogen under the effect of protonation. It is thus established, following the criterion to the optimality of the valence angles, that sp^3 nitrogen atom is the major protonation site in benzimidazole-chalcone kernels. Now, we're going to examine energitical criterion to confirm or not the above conclusion.

3.2. Energetic Parameters

The values of the proton affinityand those of the gas phase basicity calculated at HF/6-311 + G(d,p) and MPW1PW91/6-311 + G(d,p) levelsare reported respectively in the **Table 2** and **Table 3**.

All the values, of proton affinity and gas phase basicity of the different sites, reported in **Table 2** and **Table 3**, are positive, indicating that protonation reactions on the different sites are exothermic and spontaneous. Further-

Table 2. Protonation energies calculated for heteroatoms at level HF/6-311 + G(d,p) in kcal/mol.

	$N_{sp2}\text{-}H^+$		$O_{sp2}\text{-}H^+$		$N_{sp3}\text{-}H^+$	
	PA	GB	PA	GB	PA	GB
BZC-1	221.436	213.824	206.327	198.544	188.292	181.041
BZC-2	222.939	215.750	208.865	201.377	189.582	182.035
BZC-3	223.221	215.660	209.612	201.580	189.823	182.008
BZC-4	224.600	217.171	211.594	203.685	191.024	183.383
BZC-5	227.913	220.719	218.872	211.317	193.940	186.614
BZC-6	219.434	212.236	203.989	196.387	186.542	178.963
BZC-7	219.315	212.075	203.818	196.085	186.423	178.793
BZC-8	220.023	212.764	204.783	197.016	187.100	179.477
BZC-9	215.619	208.424	199.269	192.080	183.399	175.594
BZC-10	222.743	215.387	207.139	199.659	188.840	181.392

Table 3. Protonation energies calculated for heteroatoms at level MPW1PW91/6-311 + G(d,p) in kcal/mol.

	$N_{sp2}\text{-}H^+$		$O_{sp2}\text{-}H^+$		$N_{sp3}\text{-}H^+$	
	PA	GB	PA	GB	PA	GB
BZC-1	221.403	213.843	211.516	203.624	185.923	178.155
BZC-2	223.214	215.694	214.130	206.241	187.633	180.174
BZC-3	223.841	215.898	215.154	207.137	188.293	180.538
BZC-4	225.360	217.575	216.975	209.020	189.726	182.139
BZC-5	229.677	221.170	224.234	215.966	194.059	185.753
BZC-6	220.070	212.289	210.257	202.354	184.711	177.031
BZC-7	220.077	212.180	210.349	202.456	184.712	176.930
BZC-8	220.254	212.559	210.288	202.413	184.926	177.350
BZC-9	215.633	207.769	204.753	196.926	180.683	173.019
BZC-10	221.107	213.384	212.260	204.480	185.921	178.441

more, at level HF/6-311 + G(d,p), the average values (PA and GB) for N_{sp2}-H^+, O_{sp2}-H^+ and N_{sp3}-H^+ are respectively 221.724 and 214.401 kcal/mol, 207.426 and 199.773 kcal/mol and 188.496 and 180.930 kcal/mol. At MPW1PW91/6-311 + G(d,p), the average values (PA and GB) are respectively 222.063 and 214.236 kcal/mol, 212.991 and 205.061 kcal/moland 186.658 and 178.953 kcal/mol We note greater energy values on the Nsp^2 nitrogen atom compared to Osp^2 and Nsp^3. This means that oxygen atom and sp^3 nitrogen atoms are bothlessbasic sitesandthereforehave thelowestproton affinities. All the values trend to show that the sp^2 nitrogen is the major protonation site in BZC. Besides, according the energetic values, the following ascending sequence can be made: $N_{sp3} < O_{carbonyl} < N_{sp2}$. Furthermore, the percentage of protonation on each site, can be calculated. The process was the following way, depending on the below protonation reactions ((10)-(12)), respectively, with Nsp^2, $O_{carbonyl}$ and Nsp^3 leading to the complexes $BZCN_{sp2}$-H^+, $BZCO_{carbonyl}$-H^+ and $BZCN_{sp3}$-H^+, corresponding respectively to thermodynamic equilibrium constants K_1, K_2 and K_3:

$$BZC + H^+ \overset{K_1}{\rightleftarrows} BZCN_{sp2} - H^+ \quad \text{with } K_1 = \frac{\left[BZCN_{sp2} - H^+\right]}{\left[BZC\right]\cdot\left[H^+\right]} \tag{10}$$

$$BZC + H^+ \overset{K_2}{\rightleftarrows} BZCO_{carbonyl} - H^+ \quad \text{with } K_2 = \frac{\left[BZCO_{carbonyl} - H^+\right]}{\left[BZC\right]\cdot\left[H^+\right]} \tag{11}$$

$$BZC + H^+ \overset{K_3}{\rightleftarrows} BZCN_{sp3} - H^+ \quad \text{with } K_3 = \frac{\left[BZCN_{sp3} - H^+\right]}{\left[BZC\right]\cdot\left[H^+\right]} \tag{12}$$

If x_{Nsp2} is the fraction of the amount of BZC protonated with Nsp^2, the below calculation process can lead to it:

$$\begin{aligned} x_{Nsp2} &= \frac{\left[BZCN_{sp2} - H^+\right]}{\left[BZCN_{sp2} - H^+\right] + \left[BZCO_{carbonyl} - H^+\right] + \left[BZCN_{sp3} - H^+\right]} \\ &= \frac{1}{1 + \dfrac{\left[BZCO_{carbonyl} - H^+\right]}{\left[BZCN_{sp2} - H^+\right]} + \dfrac{\left[BZCN_{sp3} - H^+\right]}{\left[BZCN_{sp2} - H^+\right]}} \\ x_{Nsp2} &= \frac{1}{1 + \left(\dfrac{K_2}{K_1}\right) + \left(\dfrac{K_3}{K_1}\right)} \end{aligned} \tag{13}$$

The different equilibrium constants are calculated from variations of free enthalpies according to the relationship (14):

$$\Delta G_{298}^0 = -RT\ln\left(K\right) \text{ and } K = \exp\left(-\frac{\Delta G_{298}^0}{RT}\right) = \exp\left(\frac{GB}{RT}\right) \tag{14}$$

In the same way, the fraction of the amount of BZC protonated with $O_{carbonyl}$ is given by the below relation (15) and finally, the fraction of the amount of BZC protonated Nsp^3 is drawn according relation (16).

$$x_O = \frac{1}{1 + \left(\dfrac{K_1}{K_2}\right) + \left(\dfrac{K_3}{K_2}\right)} \tag{15}$$

and

$$x_{Nsp3} = 1 - \left(x_{Nsp2} + x_O\right) \tag{16}$$

From the results in **Table 2** and **Table 3**, one can state that BZC kernel substituents have, in practice, no effet on protonation properties of the BZC kernel, since, for a kind of heteroatom, energetic values do not really vary. So, to simplify, we'll use the average values of gas phase basicity, $\overline{GB}$, to calculate the average values of equi-

Table 4. Average gas phase basicity and protonation percentages on sp^2 nitrogen atom, carbonyl oxygen and sp^3 nitrogen atom.

	HF/6-311 + G(d.p)			MPW1PW91/6-311 + G(d.p)		
	Nsp^2	$O_{carbonyl}$	Nsp^3	Nsp^2	$O_{carbonyl}$	Nsp^3
$\overline{GB}$	214.401	199.773	180.930	214.236	205.061	178.953
$\bar{x}$ (%)	100	0	0	100	0	0

librium constants according Equation (14). Further, we'll get the average protonation percentages, $\bar{x}$ of each site using Equations ((13), (15) and (16)). Results are given in **Table 4**.

With the above average values of $\overline{GB}$ reported in **Table 4**, all the fractions K_2/K_1, K_3/K_1 and K_3/K_2 tend toward 0, whereas K_1/K_2 tends toward $+\infty$. Therefore, at level HF/6-311 + G(d,p) as well as at level MPW1PW91/6-311 + G(d,p), the average protonation percentage on sp^2 surrounds 100% when it surrounds 0% on both carbonyl oxygen and sp^3 nitrogen. Thus, according the energetic analysis, the major protonation site is strongly the sp^2 nitogen.

4. Conclusion

The aim of this work was to determine the protonation major site in benzimidazolyl-chalcone (BZC) kernel as well as its energetic characteristics. Interpreting the valence average angles around each of the three heteroatoms, it has been noticed that the sp^3 nitrogen atom is slightly the major site since the gap from ideal valence angle is the lowest. In the contrary, interpretation of energetic parameters, meaning proton affinity (PA) and gas phase basicity (GB), leads to design sp^2 nitrogen as, strongly, the major site. These conclusions are available whatever the calculation level, meaning HF/6-311 + G(d,p) or MPW1PW91/6-311 + G(d,p). Therefore, the protonation percentage on each site has been calculated. Results show that the protonation percentage surrounds 100% on sp^2 nitrogen. The conclusion is that, taking into account thermodynamic analysis, the sp^2 nitrogen is the unique protonation site in BZC. From the whole results, one can also state that BZC kernel substituents have no effect on protonation properties of the kernel, since, for a kind of heteroatom, geometric or energetic values do not really vary, although substituents vary.

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