

## DFT MODELING OF TAUTOMERIC EQUILIBRIA AND PROTON TRANSFER OF PYRAZOLONE IN GAS PHASE AND IN SOLUTION

A. Amar<sup>1</sup>, H. Meghezzi<sup>1\*</sup>, A. Boucekkine<sup>2</sup>, A. Saidoun<sup>3</sup>, Y. Rachedi<sup>3</sup> and M. Hamdi<sup>3</sup>

<sup>1</sup>Laboratoire de Thermodynamique et Modélisation Moléculaire, Faculté de chimie, U.S.T.H.B BP 32 El Alia, 16111 Bab Ezzouar, Alger, Algérie.

<sup>2</sup>UMR CNRS 6226 Sciences Chimiques de Rennes, Université de Rennes 1, Campus de Beaulieu, 35042 Rennes cedex, France.

<sup>3</sup>Laboratoire de Chimie Organique Structurale, Faculté de chimie, U.S.T.H.B BP 32 El Alia, 16111 Bab Ezzouar, Alger, Algérie.

### ABSTRACT

The tautomerism, intramolecular proton transfer and solvent effect of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one have been investigated using B3LYP/6-31G\* and B3LYP/6-311+G\*\* level of theory. The solvent effects have been simulated using the self consistent reaction field (SCRFF) method within the framework of the polarizable continuum model (PCM). The obtained results showed that among three possible tautomeric forms, the noted CH form is predominant in gas phase and solution while the OH form seems to be the less stable. The calculated equilibrium constants and molar fractions showed that the NH form is more stabilized in solution than CH and OH forms. Results of the global reactivity descriptor give the CH form more electrophilic than the two considered tautomeric forms in gas phase and in solution. In addition we note that the barrier height of the proton transfer reaction and dipole moments grow with the increase of the solvent polarity.

**Keywords:** pyrazolone, tautomerism, solvent, reactivity descriptor.

### 1. INTRODUCTION

The tautomerism of heterocycles, including important biological compounds in particular, is great of importance in many areas of chemistry and biochemistry. Knowledge of the relative stabilities of tautomeric forms of heterocycle as well as the conversion from one tautomeric form to another is important from the point of view of structural chemistry and biological activity. In addition, knowing how the tautomerization energies change in different environments, it can give an insight into the influence of solvent effects on molecular stability<sup>1,2</sup>. As a continuation of previous studies on tautomerism of the structure of biologically important heterocycles<sup>2-4</sup>, we now report on tautomerism of N-substituted pyrazolones in gas phase and in solution. Pyrazolones contain a five membered ring with two nitrogen atoms in it. The tautomerism of N-unsubstituted and N-substituted pyrazolones is an old problem and

has been the subject of a considerable number of studies<sup>5-11</sup>. It is well known that a solvent affects considerably the tautomeric equilibrium of pyrazolones<sup>12-14</sup>. In nonpolar solvents these compounds exist mainly in CH-form while in polar solvents or capable to form H-complexes they are present almost exclusively in NH or OH tautomeric forms (or both simultaneously). In this work, we have investigated the molecular structures, the tautomeric equilibria and the proton transfer in N-substituted pyrazolone by using density functional theory (DFT) and the solvent effect has been discussed. To estimate the influence of polar environment, two solvents of different dielectric constants ethanol ( $\epsilon=24$ ) and water ( $\epsilon=78$ ) were considered in our study. The structures for the titled compound are shown in figure 1. In this work we have adapted the following notation: CH form (3-methyl-1-phenyl-1H-pyrazol-5(4H)-one), OH form (3-

methyl-1-phenyl-1H-pyrazol-5-ol) and NH form (5-methyl-2-phenyl-1,2-dihydropyrazol-3-one).

## 2. COMPUTATIONAL DETAILS

All the reported calculations were performed with the Gaussian 03 program<sup>15</sup>. Full geometry optimisations were carried out using the Becke's three parameter-hybrid (B3LYP)<sup>16, 17</sup> in the DFT method with 6-31G\* and 6-311+G\*\* basis set, both in the gas phase and solvent. The stationary structures are confirmed by ascertaining that all ground states have only real frequencies and transition state have only one imaginary frequency. To estimate the solvent effect on the relative stabilities of the species, the polarized continuum model (PCM)<sup>18, 19</sup> as implemented in the Gaussian 03 suite of programs was applied. Furthermore, the natural bond orbital analysis (NBO) was carried out using optimized geometries of the tautomers in gas phase and in solution.

## 3. RESULTS AND DISCUSSION

### 3.1 Stability

Solvents effects are relevant in tautomer phenomena, since polarity differences among the tautomers can induce significant changes in their relative energies in solution. It is important to stress that the PCM model does not consider the presence of explicit solvent molecules, hence specific solute-solvent interactions are not described and the calculated solvation effects arise only from mutual solute-solvent electrostatic polarization. The total energies for the tautomers in gas phase and in solution are collected in table 1.

Our results showed the higher stability of the CH form of pyrazolone as compared to the other two forms in gas phase as well as in solution, which confirm the results of previous studies on compounds of the same class<sup>20, 21</sup>, however the OH form seems to be the less stable in all considered case. Calculations by B3LYP/6-31G\* in gas phase indicate that CH form is preferred than OH and NH forms by 10.35 Kcal/mol and 7.84 Kcal/mol respectively. In solution, with the same level of theory the CH-OH energy difference increase, it is equal to 11.23 Kcal/mol and 11.29 Kcal/mol in ethanol and water respectively. On the contrary, the CH-NH energy difference decreases considerably going from gas phase to solution. This energy difference is equal to 1.31 Kcal/mol in ethanol and 1.19 Kcal/mol in water. Moreover, our results show that the stability of all the tautomeric forms increase going from gas phase to solution and with the increase of solvent polarity. The CH form is stabilized by 6.83 Kcal/mol and 7.15 Kcal/mol going from gas phase to ethanol and

water respectively. In the same order the OH form and NH form are stabilized by 5.96 Kcal/mol, 6.21 Kcal/mol and 13.36 Kcal/mol, 13.80 Kcal/mol respectively. With extension of the basis set in B3LYP calculations, CH form remains the most stable in gas phase and solution. For the CH-OH and the CH-NH energies differences, the same tendency is observed.

### 3.2 Tautomeric equilibria

In order to confirm the predominance of one tautomeric form to another, we have considered the three tautomeric equilibria: CH/OH, CH/NH, OH/NH. The B3LYP/6-311+G\*\* calculated equilibrium constants (K) and molar fractions in gas phase and in solution are given in table 2.

As shown in table 2, the obtained results of the CH/OH equilibrium confirm the predominance of CH form compared to OH one in gas phase and in solution. The calculated molar fractions indicate that this equilibrium is shifted in favour of the OH form when going from gas phase to solution and with the increase of solvent polarity. The molar fraction of CH form decrease by  $5.41 \cdot 10^{-2}$  mol/l and  $2.21 \cdot 10^{-1}$  mol/l when going from gas phase to ethanol and water respectively. On the contrary, the molar fraction of the OH form enlarges by  $5.50 \cdot 10^{-2}$  mol/l and  $2.21 \cdot 10^{-1}$  mol/l from gas phase to ethanol and to more polar solvent (water) respectively. According to the obtained results, the CH/NH equilibrium is slightly shifted in favour of NH form when immersed in solvent. This equilibrium shift is well illustrated by the lowering of the molar fraction of CH form, which decrease by  $7.0 \cdot 10^{-4}$  mol/l and  $5.0 \cdot 10^{-3}$  mol/l going from gas phase to ethanol and water respectively; when the NH one enlarge. Results of equilibrium constants comparison show that the OH/NH equilibrium is considerably shifted in favour of NH form in solution. This shift is represented by the change in the molar fraction of NH form which becomes larger by 0.12 mol/l when immersed in solvent.

### 3.3 Global reactivity descriptors

One of the most important questions connected with the problem of reactivity of molecules in different environmental conditions is the prediction and interpretation of the preferred direction of a reaction and the product formation<sup>22</sup>. The study of molecular interactions has been a great challenge from the experimental and theoretical point of view<sup>23</sup>. Density functional theory based descriptors have found immense usefulness in the prediction of reactivity of atoms and molecules as well as site selectivity<sup>24-26</sup>. Chemical hardness ( $\eta$ ), chemical potential ( $\mu$ ) are known as global

reactivity descriptors. Using Koopmans' theorem for closed-shell molecules,  $\eta$  and  $\mu$  can be redefined as:

$$\eta = \frac{1}{2}(I - A) \approx \frac{1}{2}(\varepsilon_{LUMO} - \varepsilon_{HOMO})$$

$$\mu = -\frac{1}{2}(I + A) \approx \frac{1}{2}(\varepsilon_{HOMO} + \varepsilon_{LUMO})$$

Where  $I$  and  $A$  are the ionization potential and electron affinity of the molecules, respectively. The HOMO (highest occupied molecular orbital's) and LUMO (lowest unoccupied molecular orbital's) energies are extracted from the output file. Using  $\eta$  and  $\mu$ , Parr and al.<sup>27</sup> have defined a new quantum chemical descriptor to quantify the global electrophilic power of the molecule, known as electrophilicity index ( $\omega$ ) which is defined as:

$$\omega = \frac{\mu^2}{2\eta}$$

The B3LYP/6-311+G\*\* calculated global reactivity descriptors (hardness, chemical potential and electrophilicity) in a.u. for the studied tautomeric forms in gas phase and in solution are listed in table 3.

From table 3, the values of the global descriptors (hardness, chemical potential and electrophilicity) grow when going from gas phase to solution and with the increase of solvent polarity for the three tautomeric forms. We can see in all the cases that the hardness value is higher for the OH and lower in the case of CH form. On the contrary the absolute values of the chemical potential are higher for the CH form. When two molecules react, each one will act as an electrophile (nucleophile) and will depend on which one has a higher (lower) electrophilicity index. Based on the obtained results the electrophilicity value is higher in the CH form and lower in the OH in all the cases. Accordingly the CH form is more electrophile (less nucleophile) than the two other tautomeric forms in gas phase and in solution.

### 3.4 Proton transfer

Proton transfer reactions (PT) are important in many chemical and biological systems<sup>28-31</sup>. A large number of theoretical and experimental studies have been carried out to enrich the information regarding the possible mechanisms of PT, tautomeric equilibria and relevant properties associated with PT processes<sup>32-38</sup>. We are particularly interested in the investigation of intramolecular proton transfer in the  $CH \rightarrow OH$  proton transfer in gas phase and in solution. The structures of CH, TS and OH form for the proton transfer are shown in figure 2.

Table 4 lists the B3LYP/6-311+G\*\* Barrier height of proton transfer reaction and dipole moments in gas phase and solution. Although important selected optimized parameters at the same level of theory are summarized in table 5. Our results show that the proton transfer reaction is characterized by high activation energies in gas phase and in solution. From table 4, the reaction barrier ( $OH \rightarrow CH$ ) is equal to 63.37 Kcal/mol, 64.75 Kcal/mol and 65.01 Kcal/mol in gas phase, ethanol and water respectively. Obviously the reverse proton transfer ( $CH \rightarrow OH$ ) will proceed more difficultly than the forward reaction, because of the stability of CH form compared to the OH one. According to the obtained results, the barrier height of the proton transfer ( $CH \rightarrow OH$  and  $OH \rightarrow CH$ ) enlarge from gas phase to ethanol and to more polar solvent (water). In addition, the computed dipole moments of the CH form are larger than those of OH form in gas phase and in the two considered solvents. Furthermore, the dipole moment of the CH and OH forms grow with the increase of the solvent polarity, which is in agreement with variation trend of the stability and the barrier height of proton transfer reaction.

Selected structures parameters in table 5 indicate that the distance C1-H4 enlarges, while the one between oxygen and hydrogen (O3-H4) reduces on the CH-TS-OH proton transfer. The C1-H4 and O3-H4 distance for the transition state is 1.74Å and 1.38Å respectively. It can be concluded that the C-H bond is broken and the OH bond is formed during the proton transfer process. We note also a large distance between the hydrogen (H4) and the oxygen (O3) in the CH form and between the hydrogen (H4) and the carbon (C1) in the OH form, hence the high activation energy found for the proton transfer reaction. The optimized results show that the distance between oxygen and carbon (C1-O3) becomes larger when going from the CH to the OH form. Furthermore we see that the C1-C2 distances decrease while the C2-O3 increases when going from the CH to the OH form. It is also noticeable that the  $\langle C1-C2-O3$ ,  $\langle C1-H4-O3$  and  $\langle H4-C3-C2$  angles enlarges on  $CH \rightarrow OH$  transfer, while the  $\langle H4-C1-C2$  angle becomes shorter. The comparison of optimized parameters in different environments show that solvent has a non negligible effect mainly on the calculated bond angles, i.e.; the mean deviations from gas phase to ethanol and water respectively are 0.0194°, 0.2225°, 0.0448° and 0.0199°, 0.2334°, 0.0453° for CH, TS and OH form respectively.

According to these results, we note that the largest deviation is observed in the TS structure. The observed deviations for the bond lengths are less important compared to bond angles. Going from gas phase to ethanol and water respectively, the main deviation for the bond lengths are 0.00236 Å, 0.0043 Å, 0.0030 Å and 0.0024 Å, 0.0044 Å, 0.0032 Å for CH, TS and OH form respectively. We can also see that the largest deviation is observed in the TS structure compared to CH and OH forms.

Furthermore, NBO analysis of CH and OH tautomeric forms was carried out in gas phase and in solution. The stabilization energies between donor-acceptor orbital within CH and OH forms are presented in table 6.

The results of NBO analysis reveal somewhat changes in the stabilization of energies from the gas phase to the considered solvents. From this table we can note that the most important interaction is the electron transfer of the lone pair of N7 to the antibonding orbital C2-O3 in CH form and to the C2-C1 antibonding orbital in OH one. For both the tautomers, the lone pair of N7 is also conjugated with the antibonding

orbital C8-C9 of the phenyl ring, as well as with the N6-C5 antibonding orbital. For the first interaction, the stabilization energy is higher for the CH form, with a difference of 4.88 Kcal/mol, 11,52 Kcal/mol and 11,87 Kcal/mol compared to OH form in gas phase, in ethanol and water respectively. On the contrary, the stabilization energy in the second interaction is higher for the OH form. In addition, the electron transfer occurs from the lone pair of O3 to the C2-C1 antibonding orbital for the two tautomers. This interaction exhibits the highest  $E^{(2)}$  value of the OH form with a difference of 9.19 Kcal/mol, 12.53 Kcal/mol and 12,68 Kcal/mol compared to the CH form respectively in gas phase, in ethanol and water. The CH form is also stabilized by the interaction of the lone pair of O3 with the N7-C2 antibonding orbital. For the CH form, we note an interaction between the C2-C1 bond orbital with the N6-C5 antibonding orbital, which stabilize this tautomeric form by 28.47 Kcal/mol in gas phase, 30.17 Kcal/mol and 30,30 Kcal/mol respectively in ethanol and water.

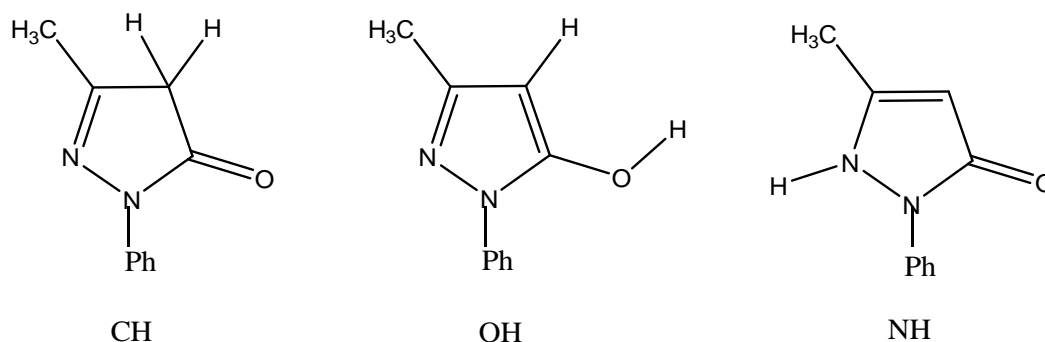


Fig. 1: tautomers under consideration

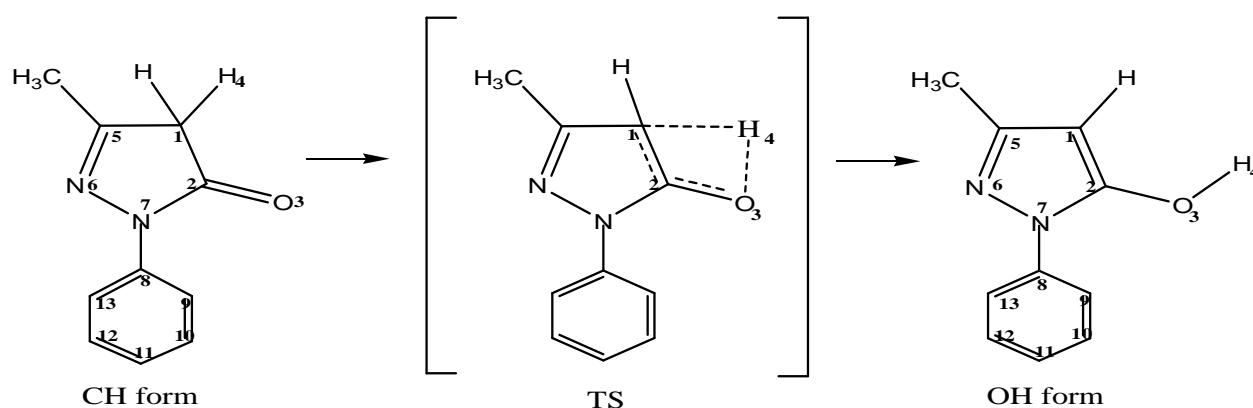


Fig. 2: structures of the CH form transition state (TS) and OH form

**Table 1: B3LYP /6-31G\* and 6-311+G\*\* calculated energies of tautomers in gas phase and in solution**

Tautomeric form	E (a.u.)					
	B3LYP/6-31G*			B3LYP/6-311+G**		
	Gas phase	Ethanol	Water	Gas phase	Ethanol	Water
CH form	-571.8026	-571.8135	-571.8140	-571.9549	-571.9652	-571.9657
OH form	-571.7861	-571.7956	-571.7960	-571.9447	-571.9547	-571.9551
NH form	-571.7901	-571.8114	-571.8121	-571.9470	-571.9614	-571.9622

**Table 2: B3LYP/6-311+G\*\* calculated equilibrium constants and molar fractions in gas phase and in solution**

Equilibrium		Gas phase		Ethanol		Water	
		K	Molar fraction	K	Molar fraction	K	Molar fraction
CH/OH	[CH]	1.19.10 <sup>-5</sup>	0.9999	5.82.10 <sup>-2</sup>	0.9449	2.84.10 <sup>-1</sup>	0.7784
	[OH]		1.19.10 <sup>-5</sup>		5.50.10 <sup>-2</sup>		2.21.10 <sup>-1</sup>
CH/NH	[CH]	8.95.10 <sup>-5</sup>	0.9999	7.31.10 <sup>-4</sup>	0.9992	5.09.10 <sup>-3</sup>	0.9949
	[NH]		8.95.10 <sup>-5</sup>		7.30.10 <sup>-4</sup>		5.06.10 <sup>-3</sup>
OH/NH	[OH]	7.48	0.1178	3.37.10 <sup>3</sup>	2.96.10 <sup>-4</sup>	4.80.10 <sup>3</sup>	2.08.10 <sup>-4</sup>
	[NH]		0.8821		0.9997		0.9998

**Table 3: B3LYP/6-311+G\*\* calculated global descriptors (in a.u.) in gas phase and in solution**

Tautomeric form	Gas phase			Ethanol			Water		
	$\eta$	$\mu$	$\omega$	$\eta$	$\mu$	$\omega$	$\eta$	$\mu$	$\omega$
CH form	0.1783	-0.2699	0.2042	0.1804	-0.2751	0.2047	0.1855	-0.2793	0.2103
OH form	0.2009	-0.2541	0.1606	0.2017	-0.2689	0.1792	0.2019	-0.2699	0.1803
NH form	0.1805	-0.2630	0.1915	0.1862	-0.2697	0.1952	0.1865	-0.2702	0.1957

**Table 4: Barrier height of proton transfer reaction (in Kcal/mol) and dipole moments (in Debye) at B3LYP/6-311+G\*\* in gas phase and solution**

	Energy barrier ( $CH \rightarrow OH$ )	Energy barrier ( $OH \rightarrow CH$ )	Dipole moments	
			CH form	OH form
Gas phase	69.77	63.37	3.56	2.65
Ethanol	71.34	64.75	4.74	3.60
Water	71.97	65.01	4.80	3.66

**Table 5: Important selected optimized parameters for CH, OH form and TS at B3LYP/6-311+G\*\* in gas phase and solution**

	Gas phase			Ethanol			Water		
	CH	TS	OH	CH	TS	OH	CH	TS	OH
Bond lengths (Å)									
C1-C2	1.5243	1.4317	1.3767	1.5173	1.4263	1.3782	1.5170	1.4260	1.3783
C2-O3	1.2125	1.2944	1.3544	1.2200	1.3030	1.3483	1.2204	1.3035	1.3481
O3-H4	2.8229	1.3826	0.9626	2.8332	1.3856	0.9650	2.8334	1.3852	0.9651
C1-H4	1.0939	1.4701	2.5837	1.0938	1.4729	2.5990	1.0938	1.4730	2.5997
C1-O3	2.4610	2.3103	2.4921	2.4621	2.3231	2.4941	2.4622	2.3235	2.4943
Bond angles (°)									
C1-C2-O3	127.7504	115.7754	131.7044	127.8402	116.6025	132.3345	127.8447	116.6244	132.3621
H4-C1-C2	110.4999	62.8655	45.6228	110.8948	61.9725	45.2681	110.9109	61.9213	45.2501
C1-H4-O3	59.6310	108.1246	73.7577	59.3338	108.6808	73.0145	59.3232	108.7306	72.9812
H4-O3-C2	45.9141	68.7712	108.7225	45.6487	67.3909	109.3697	45.6369	67.3268	109.3953

Table 6: NBO analysis of CH and OH form in gas phase and in solution

Donor NBO	Acceptor NBO	E <sup>(2)</sup> (Kcal/mol)					
		CH form			OH form		
		Gas phase	Ethanol	Water	Gas phase	Ethanol	Water
BD (C8-C9)	BD* (C13-C12)	18.94	18.64	19.61	18.89	19.34	19.36
BD (C8-C9)	BD* (C10-C11)	20.80	20.94	20.94	20.49	20.13	20.10
BD (C13-C12)	BD* (C8-C9)	20.92	21.15	21.17	21.04	21.15	21.15
BD (C13-C12)	BD* (C10-C11)	18.69	18.59	18.58	19.60	19.52	19.61
BD (C10-C11)	BD* (C8-C9)	19.66	19.64	19.64	19.85	20.43	20.46
BD (C10-C11)	BD* (C13-C12)	21.44	21.61	21.62	20.45	20.75	20.76
BD (C2-C1)	BD* (N6-C5)	/	/	/	28.47	30.17	30.30
LP (N7)	BD* (C8-C9)	30.65	32.08	32.15	25.77	20.56	20.28
LP (N7)	BD* (C2-O3)	54.48	58.36	58.54	/	/	/
LP (N7)	BD* (N6-C5)	19.95	17.35	17.24	22.66	22.40	22.38
LP (N7)	BD* (C2-C1)	/	/	/	46.35	45.98	45.94
LP (O3)	BD* (N7-C2)	27.72	26.74	26.68	/	/	/
LP (O3)	BD* (C2-C1)	20.73	19.30	19.22	29.92	31.83	31.90

E: the stabilization energy; BD\*: antibonding orbital; LP: lone pair electron.

#### 4. CONCLUSION

The tautomerism, intramolecular proton transfer and solvent effect of the N-substituted pyrazolones were theoretically investigated with the density functional theory employing the 6-31G\* and the 6-311+G\*\* basis sets. In the light of the obtained results we can conclude that among the three possible tautomeric forms, the noted CH form is predominant in gas phase and solution while the OH form seems to be the less stable. It is also noticeable that the stability of the three tautomers grows with the increase of solvent polarity. It has been shown that the studied tautomeric equilibria are solvent dependent, and that the NH form is stabilized more than CH and OH forms in all the cases. Calculated global reactivity descriptors indicate that the CH form is more electrophile than the two others tautomeric forms in gas phase and in solution. Furthermore, our results show that the proton transfer reaction is characterized by high activation energies in gas phase and in solution. In addition we note that the barrier height of the proton transfer reaction and dipole moments grow with the increase of the solvent polarity.

#### REFERENCES

- Brent, M.; Kwiatkowski, J.S.; Szabo G., Ed.; *Theoretical Chemistry of Biological Systems*, Elsevier, Amsterdam, 1986.
- Amar, A.; Meghezzi, H.; Boucekkine, A.; Kaoua, R.; Kolli, B. C. R. *Chimie*, 2010, 13, 553-560.
- Meghezzi, H.; Boucekkine, A. J. *Mol. Struct (Theochem)*, 1992, 257, 175-180.
- Ladjarafi, A.; Meghezzi, H.; Boucekkine, A. J. *Mol. Struct (Theochem)*, 2004, 709, 129-134.
- Elguero, J.; Katritzky, A.R.; Rees, C.W.; Scriven. E.F. *Comprehensive Heterocyclic Chemistry II: Pyrazoles*, Eds.; Pergamon, Oxford, 1996; vol. 3.
- Elguero, J.; Katritzky, A.R.; Denisko, O.V. *Adv. Heterocycl. Chem.* 2000, 76, 1.
- Minkin, V.I.; Garnovskii, A.D.; Elguero, J.; Katritzky, A.R.; Denisko, O.V. *Adv. Heterocycl. Chem.* 2000, 76, 157.
- Cao, M.; Teppen, B.J.; Miller, D.M.; Pranata, J.; Schafer, L. J. *Phys. Chem.* 1994, 98, 11353.
- Kataeva, O.N.; Gubaidullin, A.T.; Litvinov, I.A.; Lodochnikova, O.A.; Islamov, L.R.; Movchan, A.I.; Chimutova, G.A. *J. Mol. Struct.* 2002, 610, 175.
- Holzer, W.; Kautsch, C.; Laggner, C.; Claramunt, R.M.; Perez-Torrallba, M.; Alkorta, I.; Elguero, J. *Tetrahedron*, 2004, 60, 6791.
- Belmar, J.; Perez, F.R.; Alderete, J.; Zuniga, C.; *Braz. J. Chem. Soc.* 2005, 16, 179.
- Elguero, J.; Marzin, C.; Katritzky, A.R.; Linda, P. *The tautomerism of heterocycles*, New York, Academic Press, 1976.
- Claramunt, R.M.; Lopez, C.; Santa Maria, M.D.; Sanz, D.; Elguero, J. *Progr. Nucl. Magn. Reson. Spectr.* 2006, 49, 169.
- Luque, F.J.; Lopez-Bes, J.M.; Cemeli, J.; Aroztequi, M.; Orozco M. *Theo. Chem. Acta*, 1997, 96, 105.
- Gaussian 03, M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery Jr., R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A.

- Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P.M. W. Gill, B. Johnson, W. Chen, M.W. Wong, J.L. Andres, C. Gonzalez, M. Head-Gordon, E.S. Replogle, J.A. Pople, Gaussian, Inc., Pittsburgh, PA, 2003.
16. Becke, A.D. *Phys. Rev. A*, 1988, 38, 3098.
  17. Lee, C.; Yang, W.; Parr, R.G. *Phys. Rev. B*, 37, 1988, 787.
  18. Miertus, S.; Scrocco, E.; Tomasi, J. *J. Chem. Phys.* 1981, 55, 117.
  19. Tomasi, J.; Persico, M.; *Chem. Rev.* 1994, 94, 2027.
  20. Chmutova, G.A.; Kurbangaliev, A.R.; Vedernikov, A.N.; *Russian Journal of General Chemistry*, 2001, 71, 780-785.
  21. Toropchina, A.V.; Yanilkin, V.V.; Morozov, V.I.; Sysoeva, L.O.; Movchan, A.I.; Buzykin, B.I.; Chmutova, G.A. *Russian Journal of General Electrochemistry*, 2003, 39, 1181-1196.
  22. *Theoretical Models of Chemical Bonding: The concept of the chemical Bond*, Maksic Z.B., Ed.; Springer-Verlag: Berlin, 1990.
  23. Morokuma, K. *Acc. Chem. Res.*, 1977, 10, 294; *Molecular Interactions: From van der waals to strongly Bound Complexes*, Scheiner, S. Ed.; John-Wiley & Sons, new York, 1997.
  24. Parr, R. G. ; *Annu. Rev. Phys. Chem.* 1983, 34, 631.
  25. Parr, R.G.; Yang, W.; *Density Functional Theory of Atoms and Molecules*; Oxford University Press: Oxford, UK, 1989.
  26. Geerlings, P.; De Proft, F.; Langenaeker, W. *Chem. Rev.* 2003, 103, 1793.
  27. Parr, R. G.; Szentpaly, L. V.; Liu, S. J. *Am. Chem. Soc.* 1999, 121, 1922.
  28. Coll, M.; Frau, J.; Vilanova, B.; Llinas, A.; Donoso, J. *Int. J. Chem.* 1999, 2, 18.
  29. Madeja, F.; Havenith, M. *J. Chem. Phys.* 2002, 117, 7162.
  30. Alavi, S.; Thomson, L.D. *J. Chem. Phys.* 2002, 117, 2599.
  31. Bell, R.L.; Truong, T.N. *J. Chem. Phys.* 1994, 101, 10442.
  32. Zhanpeisov, N.U.; Cox, W.W. *J. Phys. Chem. A* 1999, 103, 4564.
  33. Shukla, M.K.; Leszczynski, J. *J. Phys. Chem. A* 2000, 104, 3021.
  34. Gorb, L.; Podolyan, Y.; Leszczynski, J.; Siebrand, W.; Fernandez-Ramos, A.; Smedarchina, Z. *Biopolymers*, 2002, 61, 77.
  35. Taylor, J.; Eliezer, I.; Sevilla, M.D. *J. Phys. Chem. B* 2001, 105, 1614.
  36. Cui, Q.; Karplus, M. *J. Phys. Chem. B* 2003, 107, 1071.
  37. Kulhánek, P.; Schlag, E.W.; Koca, J. *J. Am. Chem. Soc.* 2003, 125, 13678.
  38. Li, P.; Bu, Y.X. *J. Phys. Chem. A* 2004, 108, 10288.
  39. Sun, Y.; Li, H.R.; Liang, W.C.; Han, S.J. *J. Phys. Chem. B* 2005, 109, 591.