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Tautomerization and Substituent Effects on the Intramolecular Hydrogen Bonding in 4-Formyl-1-methylpyrazol-5-ol A Density Functional Theory

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A density functional theory (DFT) and the topology of the atoms-in-molecules (AIM) analysis has been applied to study the tautomerization and the substituent effects on the intramolecular hydrogen bonding (IHB) in the 4-formyl-1-methyl-pyrazol-5-ol and its -methyl, -amino, -hydroxyl and -fluoro derivatives. The geometries of the C3- and C6-susbtituted of the most stable enol structures were optimized at the B3LYP/6-31G+(d,p) level while their final energies were evaluated using a 6-311+G-(2df,2p) basis set expansion. Good agreement between DFT results and the published experimental results has been found. In general OH6- and F6-substitutions weaken the IHB, while the opposite is found upon Me6- and Am6-of **1a** and **2a** species. The trends observed in the relative stabilities of the enol structures do not follow the changes observed in the strength of the IHB.

Key Words: Pyrazol, Substituent effect, DFT, AIM, Intramolecular hydrogen bonding.

INTRODUCTION

Prototropic tautomerism has been widely studied in malonaldehyde[1], thiomalonaldehyde[2] and dithiomalonaldehyde[3], but not in their derivatives. 4-Acyl-1-(*n*-hexyl)-pyrazol-5-ol derivatives can be considered as malonaldehyde derivatives in which the pyrazol ring is substituted at the C1 and C2 of the malonaldehyde molecule. Recently, these ligands have been prepared and used to prepare the 4-amino-methylene derivatives, which have been used as ligands to synthesize metal complexes[4].

Belamr *et al.*[4] suggested that 4-acyl-1-(*n*-hexyl)-pyrazol-5-oles derivatives might exist in 5 different tautomeric structures resulting from the appropriate hydrogen transfer. Baesd upon ^{1}H NMR and ^{13}C NMR studies, Belamr *et al.*[4] concluded, in solution, that only one tautomeric structure is the predominant, which corresponds to the enolic structure in which a free OH group is attached to position 5 within the pyrazol ring. The stability of the enolic structures over the diketo structures is related to the existence of a stronger intramolecular hydrogen bond (IHB) and a significant

resonance-assisted hydrogen bonding (RAHB)[5]. This RAHB effect, which strengthens the H-bond, is due to the 6 π-electrons contained within the conjugated ring of these compounds, which make them potentially aromatic systems. Also, the strength of a hydrogen-bond (HB) depends on the acidity of the proton donor and the basicity of the proton acceptor.

It is well known that, substituents can affect the strength of the intramolecular hydrogen bonds (IHB) modifying the donor and acceptor abilities of the active centers of the molecule, which may transmit its electronic effect to the reaction center by the inductive effect and the resonance effect[6]. Substituent effects on the properties of many different compounds have been extensively studied for many years[7]. However, the effect of substituents on the strength of intramolecular hydrogen bonds (IHB), has been much less investigated[8-11].

The atoms in molecules (AIM) theory[12] has become a powerful tool for understanding the properties of hydrogen bonds[13-15], especially, for studying the description of the charge redistribution which takes place upon substitution. In the AIM theory, the bond critical points (bcps) of the different species were located, *i.e.*, points where the electron charge density hypersurface is minimum along the bond path connecting two nuclei of the system and maximum in the other two directions. The values of the charge density, ρ(r) and the energy density, H(r), at the bcps were useful in characterizing the IHB and its strength. It is worth remarking that the charge densities at the bcps associated with inter- and intramolecular hydrogen bonds have been shown to bear a direct relationship to the strength of the linkage[16-26]. On the other hand, a comparison of the charge density of the parent compound with those of the corresponding substituted species allowed us to analyze the electronic redistributions associated with these processes.

For the sake of simplicity, an analogue compound, 4-formyl-1-methylpyrazol-5-ol has been chosen to study the prototropic tauomerization reaction and the substituent effect on the strength of the intramolecular hydrogen bonding (IHB). In this paper, we present DFT calculations for the different tautomers of the mentioned compound, focusing on the strength of the O–H···O IHB formed. We shall also illustrate that substitution at C3 and C6 strongly affects not only the strength of the IHB, but also the strength of other chemical bonds within the system as well as the proton-transfer barriers. The strength of the HBs was estimated on the basis of the calculated relative energies of structures.

COMPUTATIONAL METHODOLOGY

In this study all calculations were performed with the Gaussian 03 package[27]. Bond lengths and angles are computed by employing the B3LYP/6-31+G(d,p) basis set. The harmonic vibrational frequencies of the different stationary points of the potential energy surface (PES) have been calculated at the same level of theory used for their optimization in order to identify the local minima and the transition states (TS), as well as to estimate the corresponding zero-point energy corrections

(ZPE) that were scaled by the empirical factor 0.9806 proposed by Scott and Radom[28]. In order to obtain more reliable energies for the local minima, final energies were evaluated by using the same functional combined with the 6-311+G(2df,2p) basis set.

The AIM analysis has been performed with the AIM2000 code[29,30], with all default options. To complete the aforementioned study, the net atomic charges were calculated using natural bond orbital (NBO) analysis[31,32].

RESULTS AND DISCUSSION

Relative stabilities of the unsubstituted species: For 4-formyl-1-methypyrazol -5-ol compound, 3 tautomers can be envisaged resulting from the appropriate hydrogen transfer[4]. Each of these isomers presents several conformers that lead, in total, to 12 structures schematized in Fig. 1. For the most stable enolic structures, the hydrogen atoms at the C3 and C6 have been substituted by 4 different groups (-methyl, -amine, -hydroxyl and -flouro). Hence, in present theoretical survey 28 structures have been optimized. All of them are local minima of the PES with all harmonic frequencies being real. For the most stable conformers of each tautomer, we have carried out a single point calculation at B3LYP/6-311+G(2df, 2p) level of theory. The corresponding total, zero point energy (ZPE) correction and the relative energies are displayed in Table-1. The optimized geometries of these 28 local minima and 9 transition states are available from the authors upon request.

TABLE-1
COMPUTED TOTAL ENERGIES, E_{tot}, (IN HARTREE), UNSCALED ZPE CORRECTIONS (IN HARTREE) AND THE RELATIVE ENERGIES INCLUDED SCALED ZPE CORRECTIONS FOR THE DIFFERENT ROTAOMERS AND TAUTOMERS OF THE UNSUBSTITUTED 1-METHYLPYRAZOL DERIVATIVES

Tautomers	[a]E_{tot}	[b]ZPE	[c]ΔE
1a	-454.2336062	0.1135800	0.0
1b	-454.2139576	0.1120910	11.4
1c	-454.2198175	0.1123530	7.9
1d	-454.2154969	0.1117710	10.3
2a	-454.2301517	0.1135640	2.2
2b	-454.2104656	0.1128010	14.0
2c	-454.2157713	0.1129840	10.8
2d	-454.2156788	0.1130700	10.9
3a	-454.2046419	0.1112900	16.8
3b	-454.2090197	0.1112880	14.0
3c	-454.2104131	0.1124650	13.9
3d	-454.2165872	0.1127200	10.2

[a]Computed at B3LYP/6-311G+(2df,2p)// B3LYP/6-31G+(d,p) level of theory. [b]Computed at B3LYP/6-31G+(d,p) level of theory. [c]All relative energies referred to 4-formyl-1-methyl pyrazol-5-ol, **1a**, tautomer. All values are in kcal/mol.

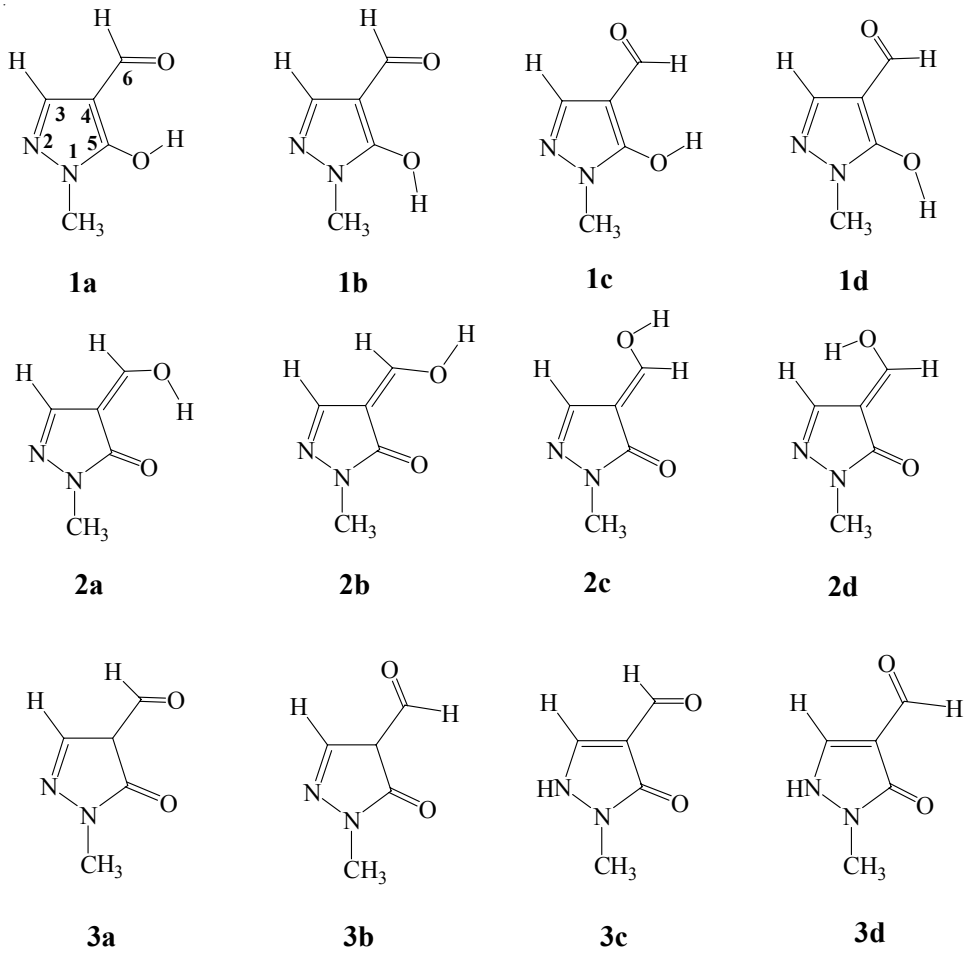


Fig. 1. Schematic representation of different rotaomers and tautomers of the 1-methypyrazol derivatives in all possible conformers

As mentioned above, 1-methylpyrazol derivatives present different tautomers that can be generated through appropriate hydrogen shifts. So in order to rationalize their intrinsic reactivity, we have to establish which tautomer is the predominant in the gas phase. Recently, Belmar *et al.*[4] showed, in solution, that the 4-formyl-1-methylpyrazol-5-ol tautomer (**1a**), is the most stable.

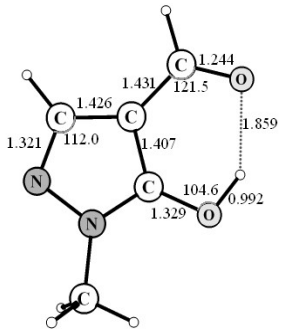
Our first result, to be noted, deduced from the relative energy calculations listed in Table-1, is that the computed order of stability of tautomers in gas phase was rated as **1a** > **2a** > **1c** > **3d** > **2d** > **3b**. In fact, present calculations indicate that the enolic structures **1a**, 4-formyl-1-methylpyrazol-5-ol and **2a**, 4-hydroxymethylene-1-methylpyrazol-5-one, are largely stable than the diketo forms. Indeed, tautomer **1a** is 2.2 kcal/mol more stable than tautomer **2a**.

These findings are in a good agreement with those experimentally suggested for 4-acyl-1-(*n*-hexyl)-3-methylpyrazol-5-ol and with those theoretically reported for thiomalonadehyde[2] and dithiomalonadehyde[3]. While they are in contrast to those theoretically reported for malonaldehyde[1], where the most stable diketo form was predicted to be slightly (0.5 kcal/mol) more stable than the most stable enol form. The stability of the enol forms over the diketo ones is due to the formation of an intramolecular hydrogen bonding (IHB), which leads to form a 6-membered ring-like structure (chelate structure). This inconsistency of the results obtained in this surevy and those reported for the malonadehyde[1] can be attributed to the presence of the pyrazol fragment attached to the positions 2 and 3 of the malonadehyde, which enhances the stability of the enol forms over the diketo forms.

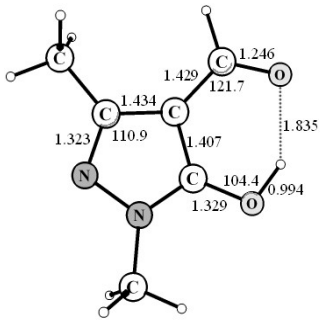
Substitution effects on molecular geometry: In the following sections, the main aim in this survey is to describe more precisely the subtituent effects on the molecular geometry and the relative stabilities of the most stable enol species **1a** and **2a**. The optimized geometries of the chelated ring substituted systems of the most stable enolic structures **1a** and **2a** are given in Fig. 2. For the sake of an easier comparison, this figure includes also the geometries of the unsubstituted tautomers **1a** and **2a** discussed in the previous section. As we have mentioned before, we have selected 4 different substituents. These substituents are $-CH_3$, $-NH_2$, -OH and -F, which model the different electronic mechanisms that can be envisaged between the substituent and the substrate. The nomenclature used to designate the different species indicates the substituent (Me = CH_3, Am = NH_2, OH and F) and the position, **C3** or **C6**, which has been substituted, according to the numbering shown in Fig. 1. Therefore **1a-Me3** and **2a-Me3** designates the enolic forms of the **C3** methyl substituted derivatives.

First inspection on the structural properties (bond lengths and bond angles) of the parent compound (unsubstituted species) shows a significant variation upon substitution. The variation in the optimized structures is found to be largely dependent on the position substituted and exclusively on the electron donor or acceptor ability of the substituent. This effect, in the bond lengths and bond angles with respect to the parent compounds, is manifested in lengthening of the single bonds and shortening of the double bonds and in accompanying changes of bond angles. Previous studies[6,26] suggested that the fluorine substitution, electron withdrawing group, systematically leads to an increase of internal angle centered at the substituted carbon, while opposite is found upon methyl substitution, electron donating group. In fact, electron withdrawing group provokes an increase of the π character of the hybrid orbital that links the carbon to the fluorine. Accordingly, the other two bonds in which the substituted carbon participated increase their σ character, leading to a larger bond angle. On Contrary, the methyl group behaves as an electron donor and the effects are the opposite.

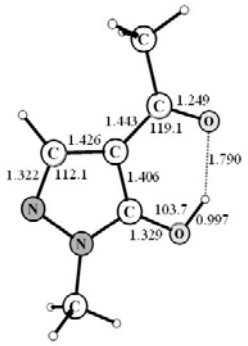
For **2a-Me6** substitution, one can see that the C4-C6 and C6=O bond lengths in **2a** approach each other. This effect is more pronounced when the substituent is



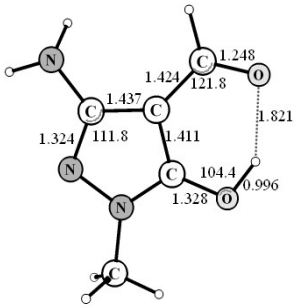
1a



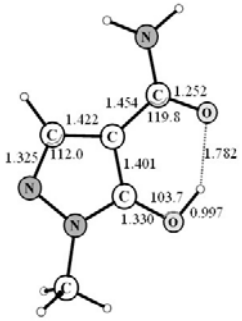
1a-Me3



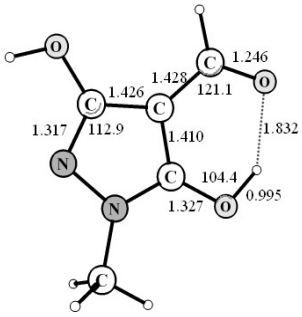
1a-Me6



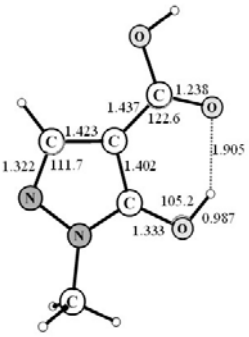
1a-Am3



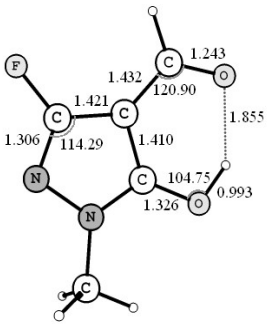
1a-Am6



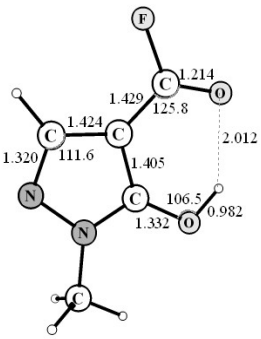
1a-OH3



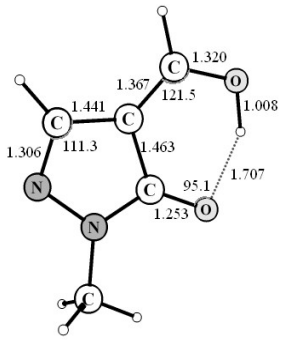
1a-OH6



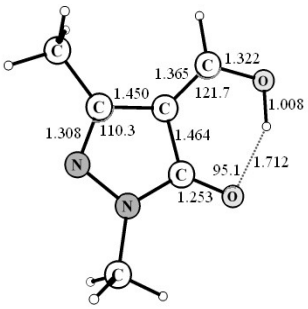
1a-F6



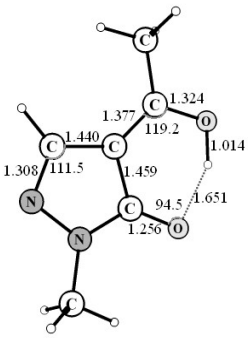
1a-F6



2a



2a-Me3



2a-Me6

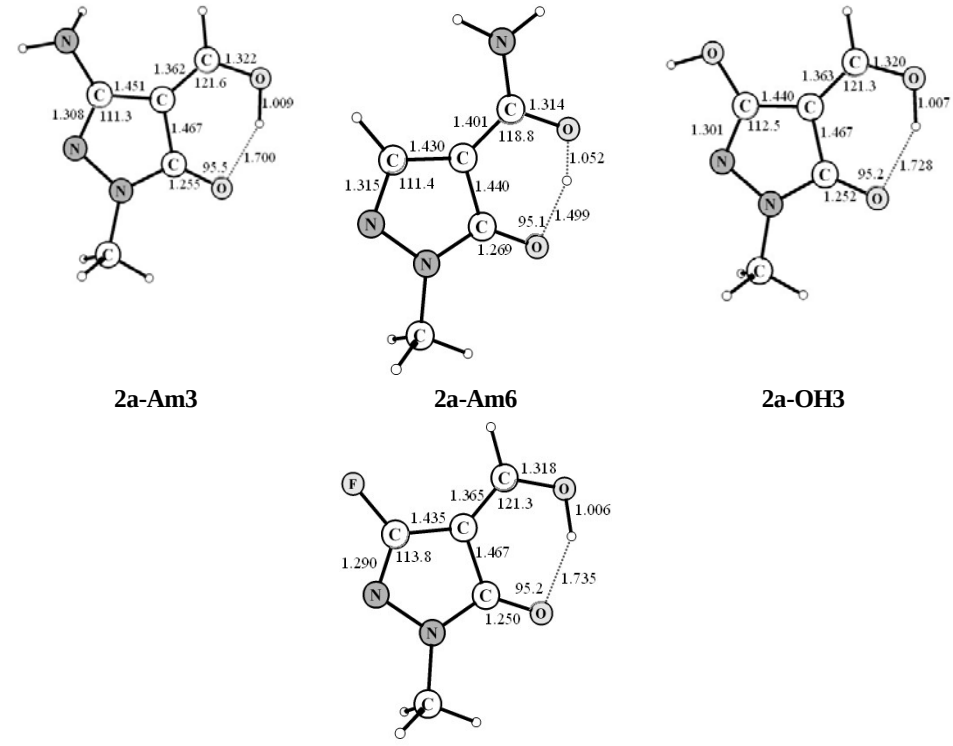


Fig. 2. B3LYP/6-31+G(d,p) optimized geometries for the different substituted **1a** and **2a** tautomers of the 1-methylpyrazol derivatives. Bond distances (Å) and bond angles (°)

an amino group, which has a lone pair of electrons. In the case of **2a-OH6** substitution, although the inductive and resonance effects are combined, the effect is less pronounced due to the higher elctronegativity of the oxygen atom. While, in case of **2a-F6** fluorine substitution effects are dominated by its σ withdrawing ability, which leads to a slight shortening of the C4-C6 and C6=O linkages. It is important noting that, in the case of methyl and amino groups, the IHB becomes significantly shorter, while a significant lengthening is observed when the other two susbstituents were considered. In fact, in the case of the -OH and -F groups, the lengthening in the IHB are about 0.046 and 0.153 Å, respectively.

C3-substitution effects are not very dramatic and the length of the C4-C6, C6=O and the IHB linkages differs very little from the parent species.

Present results show that the methyl and amine substitutions lead systematically to a decrease of the internal angle centered at the substituted carbon, C4-C6=O, while the opposite is found upon -OH and -F substitution, however, the -OH group is considered as an electron donating group, while the fluorine group is an electron withdrawing group. In fact, in case of fluorine substitution, the changing in the internal centered angle, C4-C6=O, is more pronounced.

For **2a** species, the picture is somewhat different in which the centered linkages are the C4=C6 and C6-O. In fact, Fig. 2 shows a lengthening of the C4=C6 linkage upon substitution in comparison with the parent species. This variation is more pronounced when the substituent is fluorine. On the other hand, the C6-O linkage is shortened upon substitution. This effect is also more pronounced when the substituent group is the electron withdrawing group, fluorine group.

Similarly to **1a** species, the same trends in the internal centered angle at the substituted carbon, N2=C3-C4, of the **2a** species is also observed upon substitution.

Substitution effects in the strength of the IHB: The effects of the substituents in the strength of the IHB may be quite complicated to analyze. First, the substituting group may influence the hydrogen bonding (HB) between the (C5)-OH and the (C6)=O in the **1a** tautomer and between the (C5)=O and the (C6)-OH in the **2a** tautomer by inductive effects. In this case, the electron-withdrawing or electron-donating tendency of the substituting group would be the critical factor to affect the strengths of the hydrogen bonds.

For **C3**-substituted species, this effect will be less important, because the substituting group is rather isolated from the hydrogen bond. For **C6**-substituted species, on the other hand, the substituting group is very close to the hydrogen bond between the hydroxyl and the carbonyl group and thus may directly affect the strength of the hydrogen bonding. So that, in the following, we will discuss in more details the **C6**-substitution case.

Let consider the **1a-C3** species, as indicated from present results, **C3**-substitution shortens significantly the IHB, reflecting a reinforcement of this linkage. This is also reflected in an increase of the charge density at the corresponding bond critical point, bcp, (Table-2). In addition, the computed results show that the **1a-Am3** derivative is the one which exhibits the strongest IHB. While for **2a-C3** species, disregarding the **2a-Am3**, the behaviour is completely different and the IHB becomes longer and weaker, reflected by a smaller charge densities in comparison the parent one (Table-2). Again, the computed results show that the **2a-Am3** derivative is the one which exhibits the strongest IHB.

Let us consider the **1a-C6** species, the situation is completely different in comparison to those reported for **1a-C3** species. In this case, when the substituents groups are the methyl and amino group, which act as electron-donating group, the IHB becomes shorter and stronger, reflected by a larger charge densities at bcp. While the opposite is true in the case of the hydroxyl and the fluorine groups, which act as an electron-withdrawing groups. This reinforcement of the IHB is essentially due to an increase of the donor ability of the OH group, which upon substitution becomes more acidic. This is confirmed when one compares the NBO net positive charge of the hydroxyl hydrogen in the methyl (+0.554), amine (+0.554), hydroxyl (+0.554) and fluorine (+0.553) derivatives and that in the unsubstituted **1a** form (+0.552), for more details (Table-S1) of the supplementary information.

TABLE-2
BONDING CHARACTERISTICS: CHARGE DENSITY, ρ AND ENERGY DENSITY, H(r), ALL VALUES IN ATOMIC UNITS

Bond	ρ (r)	H (r)	ρ (r)	H (r)	ρ (r)	H (r)
	1a		**1a-Me3**		**1a-Me6**	
C6=O	0.383	-0.647	0.381	-0.643	0.380	-0.641
C5-O	0.317	-0.508	0.318	-0.509	0.318	-0.510
O···H	0.034	-0.002	0.036	-0.002	0.039	-0.002
			1a-Am3		**1a-Am6**	
C6=O			0.380	-0.642	0.384	-0.659
C5-O			0.318	-0.510	0.317	-0.508
O···H			0.037	-0.002	0.040	-0.002
			1a-OH3		**1a-OH6**	
C6=O			0.381	-0.644	0.396	-0.683
C5-O			0.319	-0.512	0.315	-0.502
O···H			0.036	-0.002	0.030	-0.001
			1a-F3		**1a-F6**	
C6=O			0.384	-0.649	0.416	-0.723
C5-O			0.320	-0.514	0.314	-0.500
O···H			0.034	-0.002	0.024	-0.001
	2a		**2a-Me3**		**2a-Me6**	
C6-O	0.320	-0.514	0.319	-0.511	0.319	-0.511
C5=O	0.380	-0.647	0.380	-0.647	0.377	-0.642
O···H	0.047	-0.003	0.046	-0.002	0.054	-0.004
			2a-Am3		**2a-Am6**	
C6-O			0.319	-0.512	0.334	-0.549
C5=O			0.379	-0.645	0.367	-0.621
O···H			0.048	-0.003	0.080	-0.021
			2a-OH3		**2a-OH6**	
C6-O			0.320	-0.514	0.396	-0.683
C5=O			0.381	-0.649	0.315	-0.501
O···H			0.045	-0.002	0.030	-0.001
			2a-F3		**2a-F6**	
C6-O			0.322	-0.517	0.416	-0.723
C5=O			0.383	-0.653	0.314	-0.500
O···H			0.044	-0.002	0.024	-0.001

Consistently with present results for the **1a-C6** species, **C6** substitution in the **2a** form should increase the acidity of the OH group attached to position 6 and consequently, the strength of the IHB. This is also mirrored in the estimated bond lengths and bcp charge densities. This is also confirmed when one compares the NBO net positive charge of the hydroxyl hydrogen in the methyl (+0.550) and amine (+0.552) and that in the unsubstituted **2a** form (+0.549). These arguments indicate that the IHB upon **Am6**-substitution is more stronger than that of **Me6**-substitution. It is worth noting that no **2a-OH6** and **2a-F6** species were detected upon substitution in which **1a** is the dominant species.

TABLE-S1
COMPUTED NATURAL BOND ORBITAL CHARGES OBTAINED AT B3LYP/6-31+G(d,p), ALL VALUES ARE IN ATOMIC UNITS

	1a	**1a-Me3**	**1a-Me6**	**2a**	**2a-Me3**	**2a-Me6**
O	-0.698	-0.699	-0.706	-0.674	-0.678	-0.685
H	0.552	0.552	0.554	0.549	0.548	0.550
		1a-Am3	**1a-Am6**		**2a-Am3**	**2a-Am6**
O		-0.700	-0.709		-0.681	-0.707
H		0.551	0.554		0.549	0.552
		1a-OH3	**1a-OH6**		**2a-OH3**	**2a-OH6**
O		-0.702	-0.702		-0.675	-0.702
H		0.554	0.554		0.549	0.554
		1a-F3	**1a-F6**		**2a-F3**	**2a-F6**
O		-0.697	-0.694		-0.668	-0.694
H		0.555	0.553		0.550	0.553

Substitution effects on relative stabilities: The relative energies included the ZPE corrections of the tautomers **1a** and **2a**, together with the transition states that connect them are given in Table-3. The corresponding total energies and unscaled ZPE corrections are given in Table-S2 of the supplementary material.

TABLE-3
COMPUTED TOTAL ENERGIES, E_{tot}, (IN HARTREE), UNSCALED ZPE CORRECTIONS (IN HARTREE) AND THE RELATIVE ENERGIES, ΔE, INCLUDED SCALED ZPE CORRECTIONS OR THE STRUCTURES OF THE DIFFERENT SUBSTITUTED **1a**, **2a** AND **TS** SPECIES

Species	**1a**	**TS(1a-2a)**	**2a**
	ΔE	ΔE	ΔE
Parent	0.0	2.5	2.2
Me3	0.0	2.1	1.7
Me6	0.0	-0.8	0.0
Am3	0.0	2.0	1.6
Am6	0.0	3.1	4.2
OH3	0.0	1.9	1.3
OH6	0.0	–	–
F3	0.0	2.3	1.8
F6	0.0	–	–

As mentioned in the previous sections, the most important conclusions of present computed studies on the parent species is that tautomer **1a** is more stable than tautomer **2a**. From the results shown in Table-3, one can see that the same trend is also observed, regardless of the substituent group or position. It is worth mentioning, in the case of unsubstituted species, that tautomer **1a** is 2.2 kcal/mol more stable than tautomer **2a**. When the substitution takes place, present computed results show that the relative stabilities significantly change, but the stability trend does not change.

TABLE-S2
COMPUTED TOTAL ENERGIES, E_{tot}, (IN HARTREE) AND UNSCALED ZPE CORRECTIONS (IN HARTREE) FOR THE STRUCTURES OF THE DIFFERENT SUBSTITUTED **1a**, **2a** AND **TS** SPECIES ALL RELATIVE ENERGIES REFERRED TO **1a**

	1a		**TS**		**2a**	
	[a]E_{total}	[b]ZPE	[a]E_{total}	[b]ZPE	[a]E_{total}	[b]ZPE
Parent	-454.233606	0.113580	-454.225840	0.109724	-454.230152	0.113564
Me3	-493.568397	0.141071	-493.561171	0.137175	-493.565743	0.141099
Me6	-493.572229	0.141005	-493.565866	0.137168	-493.569775	0.141097
Am3	-509.617870	0.130338	-509.611077	0.126603	-509.615414	0.130462
Am6	-509.640950	0.130565	-509.632247	0.126733	-509.632882	0.129187
OH3	-529.490724	0.118131	-529.483939	0.114363	-529.488716	0.118261
OH6	-529.516468	0.119120	–	–	–	–
F3	-553.504054	0.105613	-553.496607	0.101791	-553.501268	0.105666
F6	-553.531149	0.106192	–	–	–	–

[a]Computed at B3LYP/6-311G+(2df,2p)// B3LYP/6-31G+(d,p) level of theory.
[b]Computed at B3LYP/6-31G+(d,p) level of theory.

However, the trends observed in the relative stabilities of the **1a** and the **2a** tautomers do not follow the changes observed in the strength of the IHB. The contrast between the trend of stability and the trend of IHB strength it might be explained easily by the fact that the IHB bond is only one bond among many others, that is, it is a part of the overall molecular system, so to be the IHB in **2a** stronger than that in **1a**, this is not at all in contrast with the trend of stability of **1a** and **2a**, where the stability of any molecular system is an overall property. The difference in strength of IHB it could be attributed to difference in molecular geometry, where each molecule has its own distribution of atoms in space and this will lead finally to different bonds lengths and strength.

Of important, one can see that, upon **Me6**-substitution, the two tautomers, **1a** and **2a**, are almost degenerate and they connected by a transition state lies at 0.8 kcal/mol below the **1a** species. However, the **1a**-unsubsituted species was 2.2 kcal/mol more stable than the **2a**-unsubstituted one. While, in case of **Am6**-susbtitution, one can see that the energy difference between the two tautomers, **1a** and **2a** is found to be larger than in the unsubstituted case. In fact, **Am6-1a** is 4.2 kcal/mol more stable than **2a** and the transition state that connects the two tautomers lies at 3.1 kcal/mol above the **1a** species.

Conclusion

From the results discussed in previous sections, it is concluded that in general the 4-formyl tautomers of the 1-methyl pyraol-5-ol, **1a** is 2.2 kcal/mol more stable than the corresponding ethanol analogue, **2a**. However, the trends observed in the relative stabilities of the **1a** and **2a** tautomers do not follow the changes observed in the strength of the IHB. It is also important to emphasize that present theoretical calculations are in excellent agreement with the experimental results.

It is also shown that the substituent effects on the IHB of 1-methyl pyrazol derivatives are not negligible, mainly when the positions substituted are **C6**, while the effects are much less pronounce when the position substituted is the carbon atom (**C3**) within the pyrazol ring.

Substituent effects on the IHB are dramatic. In general, in case of **1a**, C3-substiution implies a strengthening in the IHBs regarding of the substiutent group. While in case of **2a**, disregarding the NH_2 substiuent, substitution implies a weakening of the IHBs.

Quite importantly, in both of **1a** and **2a**, the Me-C6 and the Am-C6 substitutions imply a strengthening of the IHBs, While the opposite is observed upon OH-C6 and F-C6.

Present theoretical results showed that the substituent effects on the proton-transfer energy barriers are dramatic. While the **1a** and the **2a** forms of the unsubstituted species are separated by an energy barrier of *ca.* 2.5 kcal/mol, the substituted species at Me-C6 shows a barrier energy of -0.8 kcal/mol. That is to say that the interconversion between the **1a** and **2a** species of the Me-C6 substituted derivatives is barrier-free. Also, the two **1a** and **2a** tautomers are almost degenerate.

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