

Theoretical DFT(B3LYP)/6-31+G(d) study on the prediction of the preferred interaction site of 3-methyl-4-pyrimidone with different proton donors

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ABSTRACT

Theoretical calculations were carried out using the DFT/B3LYP/6-31+G(d) methodology in an attempt to predict the preferred interaction site of a polyfunctional heterocyclic base 3-methyl-4-pyrimidone molecule with a series of proton donors of different acidic strength, *i.e.* water, methanol, phenol, 1-naphthol, 2,4,5 trichlorophenol, pentachlorophenol, picric acid and hydrogen chloride. Computed H-bond interaction energies (ΔE_c), internuclear and intermolecular distances $r(\text{O}\cdots\text{H})$ and $r(\text{O}\cdots\text{O})$, infrared frequency shifts $\Delta\nu(\text{C}=\text{O})$ and $(\Delta\nu(\text{OH}))$ are proved to be reliable parameters for predicting the preferred interaction site of 3-methyl-4-pyrimidone. These computational data suggest that the $\text{O}-\text{H}\cdots\text{O}=\text{C}$ complex is preferred with water, methanol, phenol, 1-naphthol, 2,4,5 trichlorophenol and pentachlorophenol. However, for H-bonding with stronger acids such as picric acid or hydrochloric acid, the computational data suggest that the H-bonding occurs at the N_1 ring atom of 3-methyl-4-pyrimidone. In the $\text{O}-\text{H}\cdots\text{O}=\text{C}$ complex, where the H-bond at the carbonyl O-atom can be oriented “anti” (H_a) and “syn” (H_b) with respect to the N_3 atom, the same computational data suggest a higher stability of the “anti-O” compared to the “syn-O” orientation.

Keywords: 3-Methyl-4-Pyrimidone; DFT/B3LYP Calculation; Proton-Donor Capability

1. INTRODUCTION

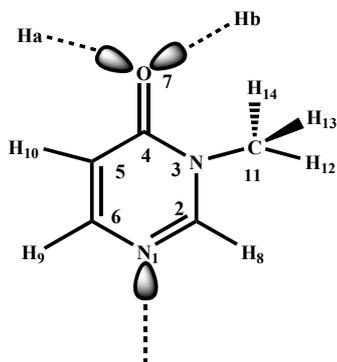
Theoretical [DFT-B3LYP/6-31+G(d)] and experimental (matrix-isolation Infrared, denoted IR, spectroscopy) investigations are suitable to discriminate between $\text{O}-\text{H}\cdots\text{N}$ and $\text{O}-\text{H}\cdots\text{O}=\text{C}$ complexes of 3-methyl-4-pyrimidone

(3M4P) and proton donors [1-4]. Experimental frequency shifts of $\nu(\text{C}=\text{O})$, $\delta(\text{C}=\text{O})$, $\gamma(\text{C}=\text{O})$ and $\nu(\text{N}_1=\text{C})$ modes of 3-methyl-4-pyrimidone, which are sensitive to H-bonding, the values of the H-bond interaction energy (ΔE_c) and the internuclear and intermolecular distances computed at the DFT(B3LYP)/6-31+G(d) level of theory have been shown that H-bonds between weak acids such as methanol are formed preferentially at the carbonyl group, whereas for stronger acids such as hydrochloric acid the complexation occurs on the N_1 atom of the ring.

In spite of these exciting results, no other, detailed studies on reliable theoretical parameters on the preferred interaction site of the polyfunctional heterocyclic base 3M4P are available in the literature. In order to identify these parameters, it is necessary to widen the range of proton donors complexing 3M4P characterized by different acidic strengths. 1-Naphthol is used here because of its rotameric properties and its possibility to form a complex with a stacking structure supported by H-bonding. Ortho-substituted chlorophenols exhibit relatively strong intramolecular $\text{OH}\cdots\text{Cl}$ H-bonds, apart from their stacking ability. Therefore, in this case, there is a competition between intramolecular and intermolecular H-bonds in the 3M4P complex that can reduce the stability of the complex. In both cases the prediction of the preferred interaction site due to only the acidity of the proton donor can be modified.

Although H-bonding between weak acids and 3M4P occurs preferentially at the carbonyl group, the most stable configuration still remains unknown. Since the oxygen atom of the carbonyl group of 3M4P has two electronic pairs oriented in the “anti” (H_a) and “syn” (H_b) directions with respect to the N_3 atom of the ring (Scheme 1), an H-bond formation with the carbonyl oxygen atom of the 3M4P can take place in both the “anti” H_a and “syn” H_b configurations, defined by the two electronic pairs of this oxygen atom.

The aim of the present study is to identify reliable



Scheme 1. 3-Methyl-4-pyrimidone.

theoretical parameters for the preferred interaction site in the 3M4P molecule with a series of proton donors with different proton-donors capabilities, and to predict the most stable configuration of the $\text{OH}\cdots\text{O}=\text{C}$ complexes, formed in most of the cases.

2. METHODOLOGY

Molecular properties such as geometries, energies and vibrational frequencies of the different monomers and H-bonded complexes were calculated by the Density Functional Theory (DFT) using the hybrid of Becke's non-local three parameter exchange and correlation functional with the Lee-Yang-Parr functional (B3LYP) [5-7]. DFT methods provide an adequate compromise between the desired chemical accuracy and the computational cost. DFT/B3LYP methods have been demonstrated in former studies to produce quite accurate results for isolated molecules modeling heterocyclic bases [8-14]. Although it is well established that H-bonding involving nucleic acid bases is not fully correctly described by DFT methods, these methods remain useful. The reason is that interactions due to H-bonding are principally electrostatic and they are reasonably well accounted for by DFT or MP2 methods [15].

In H-bond studies, the standard 6-31+G(d), 6-31++G(d), 6-31++G(d,p) and 6-311++G(d,p) basis sets have frequently been used [16-19]. For the molecular orbital expansion we have initially used the 6-31++G(d,p) basis set. The choice of this basis set was based on the consideration that, in order to obtain reliable properties for hydrogen-bonded systems, it is essential to employ basis sets of orbitals which possess sufficient diffuseness and angular flexibility [20]. Since it appeared for methanol and its homo-associates that the calculated values of the electronic energies and vibrational frequencies with the basis set 6-31+G(d) were similar to those with the larger basis set 6-31++G(d,p) [21], we have only used the former set in the further study.

As has been demonstrated by one of us for larger molecules like as nucleic acid base derivatives, selective

frequency scaling allows a reliable assignment of vibrational modes [22] the harmonic DFT frequencies were scaled with variable scaling factors, *i.e.* 0.95 for $\nu(\text{X-H})$, 0.98 for out-of-plane modes and 0.975 for all other modes. The use of different scaling factors for DFT predicted frequencies has been proposed by several authors in the past [23-25]. The infrared frequencies, intensities, and the zero-point vibrational energy (ZPE) were subsequently computed using the analytical derivatives procedure incorporated in the GAUSSIAN 03 program.

Following these calculations, the total energies E_T of the optimized structures were calculated as the sum of the electronic energy $E_{(\text{DFT})}$ and 0.975 ZPE (ZPE determined with the DFT methodology). The H-bond interaction energy of each complex was computed as the difference between the energy of the complex (cluster) and the sum of the energies of the monomer 3M4P and the proton donor. These results were corrected for the basis set superposition error (BSSE) [26], by recalculating the monomer energies in the basis set of the hetero-dimers using the Boys-Bernardi counterpoise correction [27]. The corrected H-bond interaction energy of each complex (ΔE_c) was finally computed as:

$$\Delta E_c = \left[E_{(\text{cluster})} + (0.975 \text{ZPE}_{(\text{cluster})}) \right] - \sum_i \left[E_{i(\text{monomer})} + (0.975 \text{ZPE}_{i(\text{monomer})}) \right]$$

All calculations were performed using the Gaussian 03 ab initio software package [28].

3. RESULTS AND DISCUSSION

All structural and energetic parameters for H-bonded complexes between the studied proton donors and 3M4P computed at the DFT(B3LYP)/6-31+ G(d) level are summarized in **Tables 1-4**. The geometries of the H-bonded clusters are shown in **Scheme 2**.

3.1. Prediction of the Preferred Interaction Site of 3M4P with Different Proton Donors

The analysis of the H-bond interaction energies ΔE_c in **Tables 1-4** suggests that the complex between 3M4P and the weaker proton donors such as water, methanol, phenol, 1-naphtol, 2,4,5-trichlorophenol and pentachlorophenol, are more stable for about 2.5 to 3.0 $\text{kJ}\cdot\text{mol}^{-1}$ when the H-bond interaction takes place on the $\text{C}=\text{O}$ group rather than the on the N_1 atom of the base. For the complex between 3M4P and stronger acids such as picric acid or hydrochloric acid, the stability is higher when the interaction takes place on the N_1 atom of the base rather than on the carbonyl group.

This stability difference of the complexes is confirmed by internuclear and intermolecular distances $r(\text{H}\cdots\text{O})$

Table 1. Computed DFT (B3LYP)/6-31+G(d) energetic and structural parameters of the H-bonded complexes of 3MP4 with methanol or with water at the C=O or at the N1 interaction site of the base.

	3M4P	MeOH...O=C _{anti}	MeOH...O=C _{syn}	MeOH...N _{1anti}	HOH...O=C _{anti}	HOH...O=C _{syn}	HOH...N _{1anti}
E _T	-378.891860	-494.628644	-494.628627	-494.627323	-455.326598	-455.326568	-455.325142
μ _D	2.506	3.934	1.889	1.163	3.926	1.764	1.386
ZPE	0.110180	0.163531	0.163631	0.163403	0.134447	0.134505	0.13409
ΔE _c		-25.18	-24.86	-22.56	-23.72	-23.58	-20.91
Δ(ΔE _c)		0	0.32	2.62	0	0.14	2.81
r(C=O)	1.2287	1.2386	1.2362	1.2270	1.2389	1.2363	1.2271
r(C ₅ -C ₆)	1.3648	1.3660	1.3660	1.3636	1.3660	1.3660	1.3636
r(C ₄ -C ₅)	1.4457	1.4416	1.4413	1.4465	1.4418	1.4412	1.4465
r(N ₃ -C ₂)	1.3617	1.3639	1.3627	1.3566	1.3640	1.3627	1.3565
r(N ₃ -CH ₃)	1.4648	1.4659	1.4697	1.4661	1.4659	1.4698	1.4661
r(N ₁ -C ₂)	1.3027	1.3015	1.3031	1.3066	1.3014	1.3031	1.3067
r(N ₁ -C ₆)	1.3734	1.3726	1.3707	1.3736	1.3727	1.3706	1.3733
r(N ₃ -C ₄)	1.4253	1.4141	1.4161	1.4279	1.4137	1.4160	1.4277
∠(OH...O(N))		163.46	168.53	155.67	161.57	167.55	152.80
r(O(N)...H)		1.8797	1.8845	1.9800	1.8769	1.8795	1.9794
r(O(N)...O)		2.8326	2.8491	2.9005	2.8250	2.8472	2.8864
Δr(C-O)		-0.0056	-0.0044	-0.0047			
Δr(O-H)		0.0186	0.0165	0.0183	0.0125	0.0103	0.0118
Δr(C=O)		0.0100	0.0075			0.0076	
ν(OH)		3575	3624	3572	3557	3608	3559
Δν(OH)		-190	-141	-193	-179	-128	-177
ν(C=O)	1757(8)	1730	1737	1762	1733	1740	1762
Δν(C=O)		-27	-21	-5	24	18	-5

E_T: Total Energy (a.u.); ZPE: zero-point vibrational energy (au); ΔE_c: H-bond interaction energy (kJ/mol); Δ(ΔE_c): relative H-bond energy (kJ/mol), μ: dipole moment (Debye); ν: frequency (cm⁻¹) and Δν frequency shift (cm⁻¹); r: distances (Å); ∠: angle (degree).

Table 2. Computed DFT(B3LYP)/6-31+G(d) energetic and structural parameters of the H-bonded complexes of 3MP4 with phenol or 1-naphthol at the C=O or at the N1 interaction site of the base.

	3M4P	PhOH...O=C _{anti}	PhOH...O=C _{syn}	PhOH...N _{1anti}	1NapOH...O=C _{anti}	1NapOH...O=C _{syn}	1NapOH...N _{1anti}
E _T	-378.891860	-686.386502	-686.386150	-686.384827	-840.034863	-840.034269	-840.033326
μ _D	2.506	5.494	3.937	2.525	5.944	4.478	2.637
EPZ	0.110180	0.216496	0.216532	0.216275	0.263592	0.263541	0.263445
ΔE _c		-42.72	-41.70	-38.86	-33.65	-32.23	-29.99
Δ(ΔE _c)		0	1.02	3.86	0	1.42	3.66
r(C=O)	1.2287	1.2405	1.2379	1.2257	1.2409	1.2378	1.2255
r(C ₅ -C ₆)	1.3648	1.3667	1.3663	1.3627	1.3668	1.3669	1.3626
r(C ₄ -C ₅)	1.4457	1.4396	1.4398	1.4470	1.4392	1.4393	1.4468
r(N ₃ -C ₂)	1.3617	1.3639	1.3638	1.3551	1.3639	1.3627	1.3547
r(N ₃ -C ₂)	1.4648	1.4669	1.4690	1.4666	1.4672	1.4692	1.4667
r(N ₁ -C ₂)	1.3027	1.3019	1.3024	1.3065	1.3020	1.3032	1.3066
r(N ₁ -C ₆)	1.3734	1.3711	1.3704	1.3752	1.3708	1.3696	1.3754
r(N ₃ -C ₄)	1.4253	1.4114	1.4135	1.4297	1.4110	1.4144	1.4303
∠(OH...O(N))		168.55	172.05	169.12	169.95	158.00	170.83

Continued

r(O(N)···H)		1.8000	1.8160	1.8924	1.7954	1.8522	1.8789
r(O(N)···O)		2.7728	2.7919	2.8677	2.7716	2.8224	2.8587
$\Delta r(\text{C-O})$		-0.0303	-0.0280	-0.0302	-0.0111	-0.0081	-0.0115
$\Delta r(\text{O-H})$		0.0206	0.0172	0.0221	0.0162	0.0077	0.0183
$\Delta r(\text{C=O})$		0.0118	0.0092	-0.0030	0.0122	0.0090	-0.0032
$\nu(\text{OH})$		3461	3537	3419	3452	3525	3394
$\Delta\nu(\text{OH})$		-283	-207	-325	-305	-232	-363
$\nu(\text{C=O})$	1757(8)	1726	1734	1766	1724	1731	1767
$\Delta\nu(\text{C=O})$		-31	-23	+9	-33	-26	+10

E_T : Total Energy (a.u.); ZPE: zero-point vibrational energy (au); ΔE_c : H-bond interaction energy (kJ/mol); $\Delta(\Delta E_c)$: relative H-bond energy (kJ/mol), μ : dipole moment (Debye); ν : frequency (cm^{-1}) and $\Delta\nu$ frequency shift (cm^{-1}); r: distances (Å); θ : angle (degree).

Table 3. Computed DFT (B3LYP)/6-31+G(d) energetic and structural parameters of the H-bonded complexes of 3MP4 with 2,4,5-trichlorophenol (2,4,5-TCP) or pentachlorophenol (PCP) at the C=O or at the N_1 interaction site of the base.

	3M4P	2,4,5 TCP···O=C _{anti}	2,4,5 TCP···O=C _{syn}	2,4,5 TCP···N ₁	PCP···O=C _{anti}	PCP···O=C _{syn}	PCP···N ₁
E_T	-378.891860	-2065.166744	-2065.163324	-2065.163843	-2984.335163	-2984.333705	-2984.333129
μ_D	2.506	7.594	5.114	4.053	6.762	4.951	3.636
EPZ	0.110180	0.187827	0.186403	0.187418	0.167755	0.167724	0.167493
ΔE_c		-32.75	-27.41	-26.18	-33.34	-29.59	-28.67
$\Delta(\Delta E_c)$		0	5.34	6.57	0	3.75	4.67
r(C=O)	1.2287	1.2432	1.2362	1.2245	1.2415	1.2373	1.2255
r(C ₅ -C ₆)	1.3648	1.3675	1.3661	1.3618	1.3669	1.3662	1.3624
r(C ₄ -C ₅)	1.4457	1.4373	1.4407	1.4474	1.4391	1.4401	1.4465
r(N ₃ -C ₂)	1.3617	1.3642	1.3637	1.3531	1.3639	1.3638	1.3547
r(N ₃ -CH ₃)	1.4648	1.4680	1.4680	1.4672	1.4672	1.4685	1.4665
r(N ₁ -C ₂)	1.3027	1.3021	1.3023	1.3077	1.3019	1.3024	1.3058
r(N ₁ -C ₆)	1.3734	1.3697	1.3709	1.3765	1.3708	1.3705	1.3765
r(N ₃ -C ₄)	1.4253	1.4082	1.4149	1.4316	1.4109	1.4138	1.4305
$\theta(\text{OH} \cdots \text{O}(\text{N}))$		175.82	152.29	173.56	151.35	151.10	148.08
r(O(N)···H)		1.7359	1.7693	1.8257	1.7878	1.8485	1.8614
r(O(N)···O)		2.7147	2.7784	2.8155	2.70141	2.7532	2.7573
$\Delta r(\text{C-O})$		-0.0101		-0.0098	-0.0119	-0.0095	-0.0125
$\Delta r(\text{O-H})$		0.0170		0.0202	0.0188	0.0119	0.0217
$\Delta r(\text{C=O})$		0.0145	0.0075	-0.0042	0.0128	0.0086	-0.0032
$\nu(\text{OH})$		3362	3433	3284	3341	3403	3270
$\Delta\nu(\text{OH})$		333	262	411	343	281	414
$\nu(\text{C=O})$	1757(8)	1720	1730	1770	1725	1737	1768
$\Delta\nu(\text{C=O})$		-37	-27	+12	-32	-20	+10

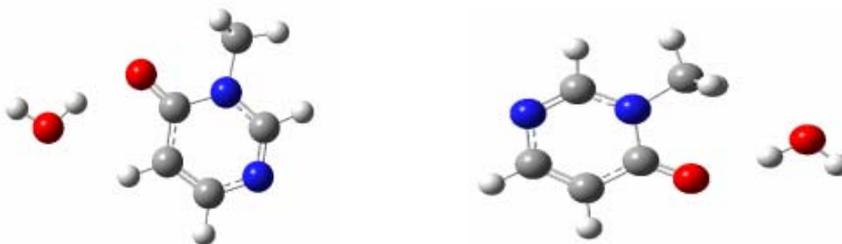
E_T : Total Energy (a.u.); ZPE: zero-point vibrational energy (a.u.); ΔE_c : H-bond interaction energy (kJ/mol); $\Delta(\Delta E_c)$: relative H-bond energy (kJ/mol), μ : dipole moment (Debye); ν : frequency (cm^{-1}) and $\Delta\nu$ frequency shift (cm^{-1}); r: distances (Å); θ : angle (degree).

Table 4. Computed DFT(B3LYP)/6-31+G(d) energetic and structural parameters of the H-bonded complexes of 3MP4 with picric acid (APQ) or hydrochloric acid at the C=O or at the N₁ interaction site of the base.

	3M4P	APQ...O=C _{anti}	APQ...O=C _{syn}	APQ...N _{1anti}	HCl...O=C _{anti}	HCl...O=C _{syn}	HCl...N _{1anti}
E _T	-378.891860	-1299.897507		-1299.897781	-839.703010	-839.701325	-839.703168
μ _D	2.506	6.405		3.815	6.009	4.439	3.262
EPZ	0.110180	0.222578		0.222306	0.119304	0.1191	0.119081
ΔE _c		-107.49		-109.08	-28.20	-24.30	-29.20
Δ(ΔE _c)		2.31		0	1.00	4.90	0
r(C=O)	1.2287	1.2402		1.2258	1.4191	1.2381	1.2249
r(C ₅ -C ₆)	1.3648	1.3671		1.3624	1.3671	1.3661	1.3621
r(C ₄ -C ₅)	1.4457	1.4397		1.4467	1.4384	1.4400	1.4475
r(N ₃ -C ₂)	1.3617	1.3634		1.3540	1.3637	1.3645	1.3532
r(N ₃ -CH ₃)	1.4648	1.4673		1.4665	1.4677	1.4680	1.4669
r(N ₁ -C ₂)	1.3027	1.3022		1.3073	1.3022	1.3019	1.3059
r(N ₁ -C ₆)	1.3734	1.3709		1.3763	1.3703	1.3708	1.3742
r(N ₃ -C ₄)	1.4253	1.4124		1.4303	1.4102	1.4132	1.4316
∠(OH...O(N))		137.84		142.10	176.53	177.86	179.91
r(O(N)...H)		1.8400		1.8249	1.7319	1.7752	1.7315
r(O(N)...O)		2.6665		2.6940	3.0791	3.1107	3.0593
Δr(C-O)		-0.0359		-0.0377			
Δr(O-H)		0.0278		0.0382	0.0384	0.0256	0.0572
Δr(C=O)		0.0115			0.0132	0.0094	0.0038
ν(OH)		3267		3054	2410	2475	2149
Δν(OH)		-480		-693	-511	-446	-772
ν(C=O)	1757(8)	1729		1766	1717	1729	1767
Δν(C=O)		-28		+9	-40	-29	+10

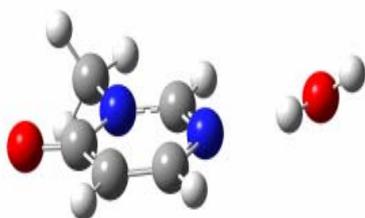
E_T: Total Energy (au); ZPE: zero-point vibrational energy (a.u.); ΔE_c: H-bond interaction energy (kJ/mol); Δ(ΔE_c): relative H-bond energy (kJ/mol), μ: dipole moment (Debye); ν: frequency (cm⁻¹) and Δν frequency shift (cm⁻¹); r: distances (Å); ∠: angle (degree); APQ: picric acid.

Water-3M4P (ΔE_c, kJ/mol)

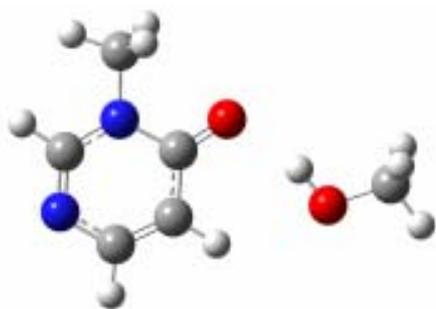
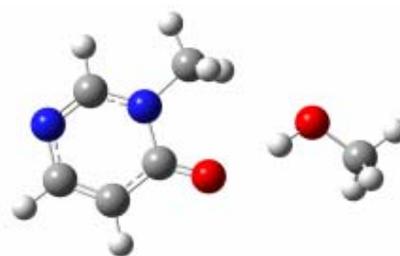
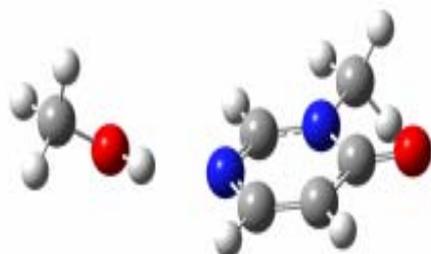
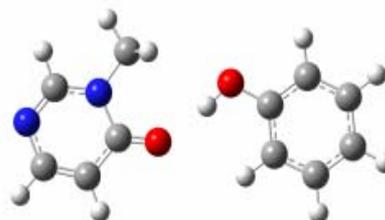
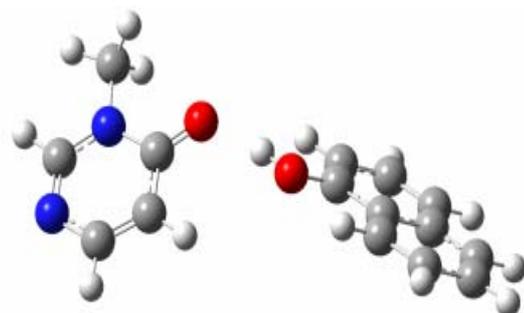


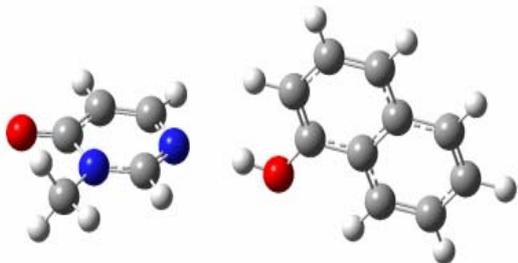
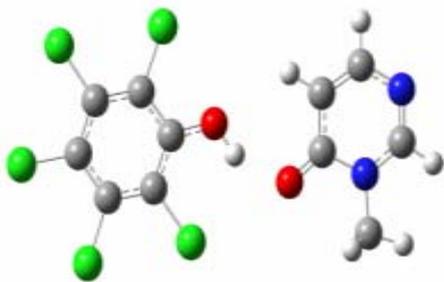
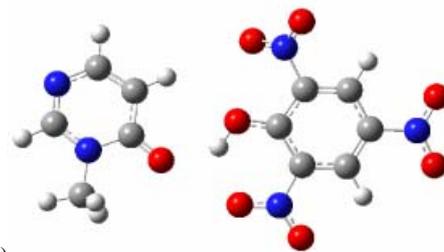
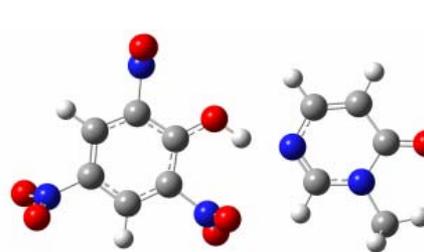
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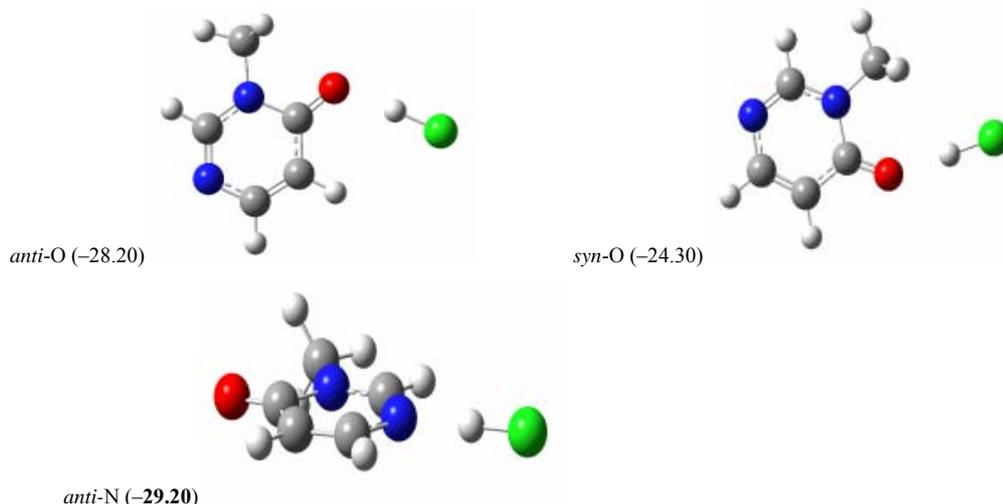
syn-O (-23.58)



anti-N (-20.91)

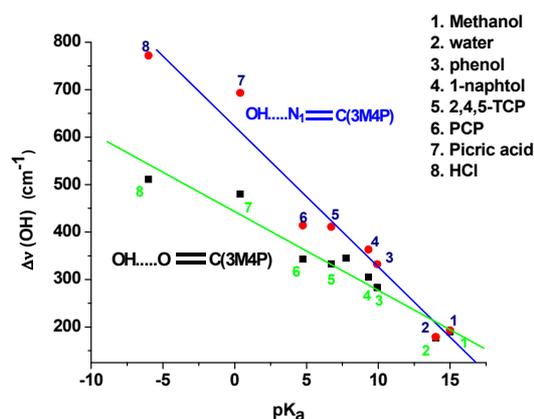
Methanol-3M4P (ΔE_c , kJ/mol)*anti-O* (-25.18)*syn-O* (-24.86)*anti-N* (-22.56)**Phenol-3M4P (ΔE_c , kJ/mol)***anti-O* (-42.60)*syn-O* (-41.60)*anti-N* (-38.75)**1-Naphtol-3M4P (ΔE_c , kJ/mol)***anti-O* (-33.66)

anti-N (-30.00)**2,4,5-Trichlorophenol-3M4P (ΔE_c , kJ/mol)***anti*-O (-32.75)*anti*-N (-26.18)**Pentachlorophenol-3M4P (ΔE_c , kJ/mol)***anti*-O (-33.34)*syn*-O (-29.59)*anti*-N (-28.67)**Picric acid-3M4P (ΔE_c , kJ/mol)***anti*-O (-107.49)*anti*-N (-109.08)

Hydrochloric acid-3M4P (ΔE_c , kJ/mol)**Scheme 2.** Clusters of 3M4P with different proton donors (in red O, blue N, black C, green Cl, and grey H).

and $r(\text{O}\cdots\text{O})$ which become shorter when the complex is more stable, *i.e.* when the H-bond interaction occurs at the C=O group with all proton donors, except for picric acid and hydrochloric acid. The frequency shift of the $\nu(\text{C}=\text{O})$ mode of a polyfunctional heterocyclic base such as 3M4P can also be used as an indication on the selectivity of the H-bond interaction in the base. A frequency decrease of $\nu(\text{C}=\text{O})$ suggests an interaction on the carbonyl site, whereas a frequency increase suggests a preferential interaction on the N_1 atom of the base. The analysis of the calculated $\Delta\nu(\text{C}=\text{O})$ values in **Tables 1-4** confirms the preference of 3M4P to interact with water, methanol, phenol, 1-naphthol, 2,4,5-trichlorophenol or pentachlorophenol by its C=O function, but with picric acid or hydrochloric acid by its N_1 atom.

According to Allen [29], for the same H-bond enthalpy values, the $\Delta\nu(\text{OH})$ value is larger for $\text{OH}\cdots\text{N}$ than for $\text{OH}\cdots\text{O}=\text{C}$ H-bonds, which is due to a greater charge transfer contribution in $\text{OH}\cdots\text{N}$ than in $\text{OH}\cdots\text{O}=\text{C}$ bonds. This is illustrated in **Figure 1**, which relates $\Delta\nu(\text{OH})$ with pK_a values of the different proton donors. Thus, a value of the shift $\Delta\nu(\text{OH})$ as large as -650 to -700 cm^{-1} suggests a H-bond interaction on the N atom. For the complexes between 3M4P and picric or hydrochloric acid, the calculated $\Delta\nu(\text{OH})$ values of -693 and -772 cm^{-1} , respectively, undoubtedly demonstrate $\text{HC}\cdots\text{N}$ and $\text{OH}\cdots\text{N}$ interactions. The frequency shift difference $\Delta[\Delta\nu(\text{OH})] = [\Delta\nu(\text{OH})_{\text{N}} - \Delta\nu(\text{OH})_{\text{O}}]$ can be used as a more precise indication for the selectivity of the H-bond interaction in heterocyclic polyfunctional bases. The shift differences $\Delta[\Delta\nu(\text{OH})]$ listed in **Table 5** appear to be smaller than -100 cm^{-1} for all complexes of 3M4P at the C=O group, whereas the values are larger than -200 cm^{-1} for the complexes at the N_1 atom.

**Figure 1.** $\Delta\nu(\text{OH})$ values of 3M4P complexes against pK_a values of the proton donors.**Table 5.** Computed DFT(B3LYP)/6-31+G(d) frequency shifts $\Delta\nu(\text{C}=\text{O})$ and shift differences $\Delta[\Delta\nu(\text{OH})]$ of the most stable complexes of 3MP4 with different proton donors.

Proton donors	pK_a	$\Delta\nu(\text{C}=\text{O})$ of 3MP4 (cm^{-1})	$\Delta(\Delta\nu(\text{OH}))$ of proton donor (cm^{-1})
Water	14	-24	-2
Methanol	15	-27	-3
Phenol	9.92	-31	-49
1-Naphthol	9.32	-34	-58
2,4,5-Trichlorophenol	6.72	-37	-78
Pentachlorophenol	4.74	-33	-71
Picric acid	0.38	+8	-213
Hydrochloric acid	-6	+10	-261

For the complexes which are more stable when the H-bond interaction takes place on the carbonyl site rather than on the N_1 atom of the base, a plot of $\Delta\nu(\text{C}=\text{O})$ against pK_a of the proton donors is illustrated in **Figure 2**. It is observed that the parameter $\Delta\nu(\text{C}=\text{O})$ increases with increasing acidity of proton donor, until a pK_a value of around 6.7 and then decreases with increasing acidity. The sequence of the $\Delta\nu(\text{C}=\text{O})$ values are: water < methanol < phenol < 1-naphtol < 2,4,5-trichlorophenol > pentachlorophenol. Other parameters, e.g. the shift $\Delta\nu(\text{OH})$ and the relative energy between both sites [$\Delta(\Delta E_c)$] vary in a fairly similar way.

As shown in **Figure 2**, the pentachlorophenol which is classified as a strong proton donor by its small pK_a value (4.6), has a weak value of $\Delta\nu(\text{C}=\text{O})$, suggesting a unexpected weaker interaction with 3M4P.

$\text{OH}\cdots\text{Cl}$ intramolecular and $\text{OH}\cdots\text{O}=\text{C}$ intermolecular H-bonds in the pentachlorophenol-3M4P complex, which reduces the stability of the latter complex. Since the pentachlorophenol is twice ortho-substituted with Cl, it is not surprising to observe strong intramolecular $\text{OH}\cdots\text{Cl}$ H-bonding.

3.2. Stability of “anti-O” and “syn-O” Conformations

For the complexes between 3M4P and weak proton donors, which are formed preferentially at the carbonyl group, the comparison of H-bond interaction energies ΔE_c in **Table 5** illustrates that the “anti-O” complexes are more stable than the “syn-O” complexes. The H-bond interaction energies ΔE_c decrease in the order *anti-O* > *syn-O* > *anti-N*. On the other hand, for the complexes between 3M4P and stronger acids such as picric acid or hydrochloric acid the H-bond interaction energies ΔE_c decrease in the order *anti-O* > *syn-O* > *anti-N*. For the stronger donors, the polarization of the O-H bond becomes more accentuated and induces a strong electronic repulsion between the proton donor O atom and the N3 atom of the base in the “syn-O” orientation (**Scheme 3**). This polarization of the O-H bond becomes too small for the weak proton donors, resulting in a negligible electronic repulsion.

In addition to the H-bond interaction energy ΔE_c , the shifts of the $\nu(\text{C}=\text{O})$ and $\nu(\text{OH})$ modes as well as the internuclear and intermolecular distances $r(\text{O}\cdots\text{H})$ and $r(\text{O}\cdots\text{O})$ listed in **Table 6** confirm the higher energetic stability of the “anti-O” complexes with 3M4P as compared to the “syn-O” complexes. For the complexes between 3M4P and weak proton donors the shifts $\Delta\nu(\text{C}=\text{O})$ and $\Delta\nu(\text{OH})$ decrease as *anti-O* > *syn-O* while the internuclear and intermolecular distances $r(\text{O}\cdots\text{H})$ and $r(\text{O}\cdots\text{O})$ increase as *anti-O* < *syn-O* < *anti-N*. A reverse effect is found for the complexes between 3M4P and the stronger acids, the internuclear and intermolecular

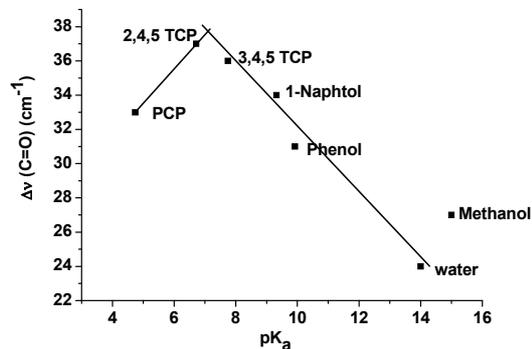
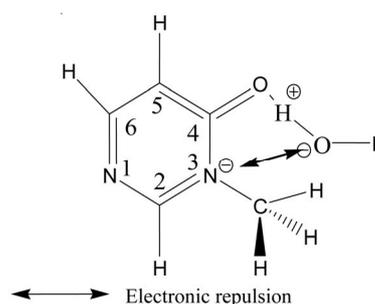


Figure 2. $\Delta\nu(\text{C}=\text{O})$ of 3M4P against the pK_a value of the proton donors for $\text{C}=\text{O}\cdots\text{H}-\text{O}$ complexes of 3M4P 2,4,5-TCP: 2,4,5-trichlorophenol; 3,4,5-TCP: 3,4,5-trichlorophenol; PCP: pentachlorophenol.



Scheme 3. Electronic repulsion in “syn” (H_b) $\text{C}=\text{O}\cdots\text{H}-\text{O}$ complexes.

distances $r(\text{O}\cdots\text{H})$ and $r(\text{O}\cdots\text{O})$ increasing as *anti-N* < *anti-O* < *syn-O*.

4. CONCLUSION

Theoretical (DFT-B3LYP/6-31+G(d)) calculations were performed to predict the preferred interaction site of the polyfunctional heterocyclic base 3-methyl-4-pyrimidone with proton donors of different acidic strength (water, methanol, phenol, 1-naphtol, 2,4,5-trichlorophenol, pentachlorophenol, picric acid and hydrochloric acid). Special attention has been paid to the H-bond interaction energy (ΔE_c), the internuclear and intermolecular distances, the shifts $\Delta\nu(\text{C}=\text{O})$ and $\Delta\nu(\text{OH})$ and the shift difference parameter $\Delta[\Delta\nu(\text{OH})]$. The computational data were proved to be reliable for predicting the preferred interaction site of the 3-methyl-4-pyrimidone molecule with proton donors. The complexes of 3-methyl-4-pyrimidone and water, methanol, phenol, 1-naphtol, 2,4,5-trichlorophenol and pentachlorophenol are more stable when the H-bond interaction takes place on the $\text{C}=\text{O}$ function rather than on the N_1 atom of the base. At the contrary, for the complex between 3-methyl-4-pyrimidone and the stronger acids picric acid and hydrochloric acid, the stability is higher when the interaction takes place on the $N(1)$ atom of the base. For the complexes

Table 6. Summary of computed DFT(B3LYP)/6-31+G(d) energetic and structural parameters of the H-bonded complexes of 3MP4 with proton donors at the C=O or at the N₁ interaction site of the base.

Parameter	Proton donor	Structure anti-O=C	Structure syn-O=C	Structure anti-N ₁
r(H...O(N)) (Å)	Water	1.874	1.880	1.979
	Methanol	1.880	1.884	1.980
	Phenol	1.800	1.816	1.888
	1-Naphthol	1.795	1.852	1.879
	2,4,5-Trichlorophenol	1.736	1.769	1.826
	Pentachlorophenol	1.788	1.849	1.861
	Picric acid	1.740		1.733
	Hydrochloric acid	1.732	1.775	1.731
r(O(Cl)...O(N)) (Å)	Water	2.825	2.847	2.886
	Methanol	2.833	2.849	2.901
	Phenol	2.773	2.792	2.868
	1-Naphthol	2.772	2.822	2.859
	2,4,5-Trichlorophenol	2.712	2.778	2.816
	Pentachlorophenol	2.701	2.753	2.757
	Picric acid	2.694		2.667
	Hydrochloric acid	3.079	3.111	3.059
ΔE _c (kJ/mol)	Water	23.80	23.58	20.91
	Methanol	25.18	24.86	22.56
	Phenol	42.72	41.70	38.86
	1-Naphthol	33.66	32.23	30.00
	2,4,5-Trichlorophenol	32.75	27.41	26.18
	Pentachlorophenol	33.34	29.59	28.67
	Picric acid	107.50		109.08
	Hydrochloric acid	28.20	24.30	29.20
Δν(C=O) (cm ⁻¹)	Water	-24	-18	+5
	Methanol	-27	-21	+5
	Phenol	-31	-24	+9
	1-Naphthol	-34	-26	+9
	2,4,5-Trichlorophenol	-37	-27	+12
	Pentachlorophenol	-33	-21	+10
	Picric acid	-35		+8
	Hydrochloric acid	-40	-29	+10
Δν(HO(Cl)) (cm ⁻¹)	Water	177	128	179
	Methanol	190	141	193
	Phenol	283	207	332
	1-Naphthol	305	232	363
	2,4,5-Trichlorophenol	333	262	411
	Pentachlorophenol	343	281	414
	Picric acid	480		693
	Hydrochloric acid	511	446	772

between weak acids and 3-methyl-4-pyrimidone, which are formed preferentially at the carbonyl group, “anti” and “syn” complexes are possible, since the O atom of the group has two electronic pairs oriented in the directions (H_a and H_b) of the N_3 atom of the ring. The H-bond interaction energies ΔE_c , the shifts $\Delta\nu(C=O)$ and $\Delta\nu(OH)$ and the internuclear and intermolecular distances $r(O\cdots H)$ and $r(O\cdots O)$ all suggest a larger stability of the “anti-O” than of the “syn-O” complexes.

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