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RESEARCH ARTICLE

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Tautomerism of pyridinylbutane-1,3-diones: An NMR and DFT study

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Abstract

The three possible 1-(n-pyridinyl)butane-1,3-diones (**nPM**) have been synthesized. Structures, tautomerism, and conformations are investigated by means of DFT calculations. ^{1}H and ^{13}C NMR spectra are assigned, and deuterium isotope effects on ^{13}C chemical shifts have been measured. Analysis of the isotope effects leads to the equilibrium constants of the keto–enol tautomers. Some interesting differences are seen between the three compounds and the phenyl analogs. The isotope effects can also rank the hydrogen bonds of the compounds, with the one with nitrogen in the three positions of the pyridine ring as the weakest. Structures, conformers, energies, and NMR nuclear shieldings are calculated using DFT calculations at the B3LYP/6-311++G(d,p) level.

KEYWORDS

DFT calculations, hydrogen bonding, isotope effects on chemical shifts, NMR, pyridinylbutane-1,3-diones, tautomerism, β-diketones

1 | INTRODUCTION

β-Diketones have been investigated because of their strong intramolecular hydrogen bonds of the keto–enol-forms, the low barrier interconversion between the keto–enol tautomers,[1] as building blocks for the synthesis.[2,3] β-diketones also form the backbone of the biologically interesting curcuminoids.[4,5] Recently, their biological properties have been reviewed.[6–8] β-diketones may exist both on the diketo-form and on keto–enol forms (see Figures 1 and 2 for different keto–enol tautomers and conformers). The tautomerism between the diketo- and keto–enol-forms is slow on the NMR timescale. The tautomerism between keto–enol- and diketo-forms of β-diketones has attracted attention, and the equilibrium constants have been determined for a series of compounds, including heteroaromatic substituents such as thiophenyl and 4-N pyridinyl.[9,10] These studies were conducted in an aqueous solution with ionic strength of 0.1 at 25°C. The diketo, keto–enol equilibrium is of less importance in this study as it is only found in one compound. The present study concentrates on the equilibrium between keto–enol tautomers (see Figure 1b). A recent paper investigated the equilibrium of pyridoylbenzoylmethanes in the liquid and in the solid state and found some unusual equilibrium differences among the different isomers and between the liquid and the solid state.[11] This spurred the synthesis of the present compounds with a methyl group in one end (see Figure 1). A convenient way of investigating equilibria in systems close to 1:1 is to study deuterium isotope effects on ^{13}C chemical shifts.[12] The synthesis of 1-(3-pyridinyl)butane-1,3-dione was performed as described in the literature.[13]

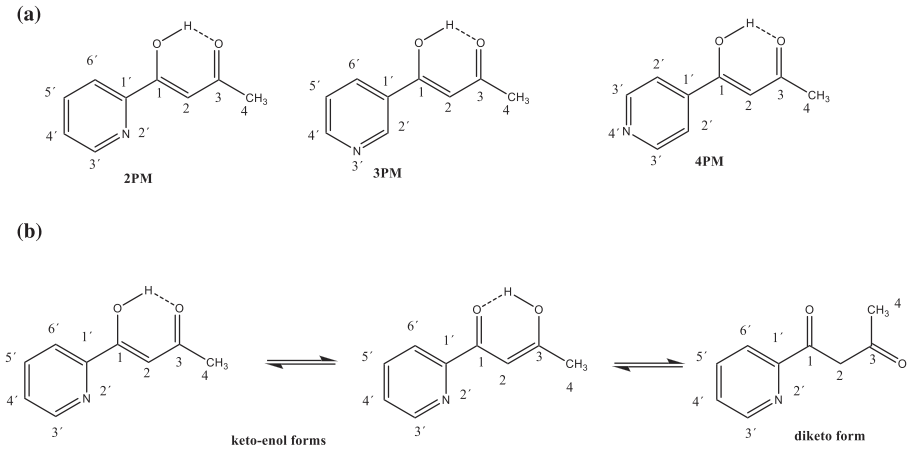

FIGURE 1 (a) Compounds. (b) Tautomeric equilibria between keto–enol-forms and the corresponding diketo-form illustrated for **2PM**.

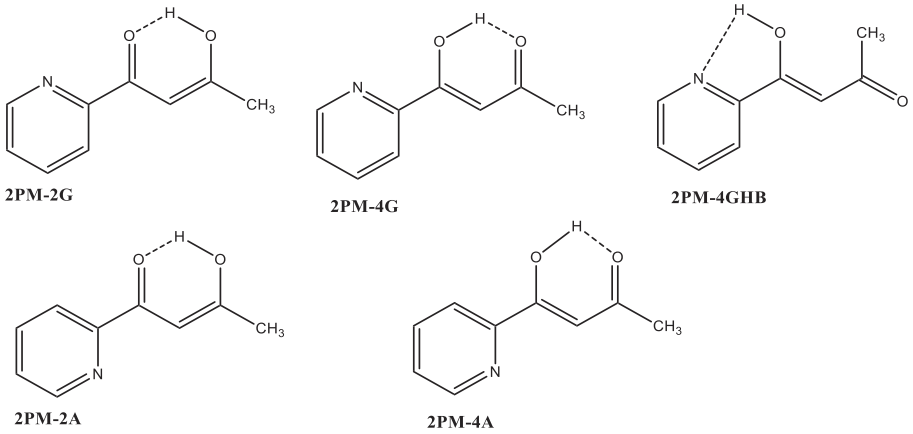

FIGURE 2 Nomenclature. Depending on the position, the indicated nitrogen can be either gauche (G) (nitrogen same side as the C = O) or anti (a) illustrated for **2PM**. For **2PM,** also hydrogen bonding to nitrogen is possible **2PM-4GHB**.

2 | EXPERIMENTAL

2.1 | Compounds

Synthesis and NMR data of the three 1-(n-pyridinyl) butane-1,3-diones are given in the Supporting Information.

2.2 | NMR

The NMR spectra were obtained on Avance Bruker-500 MHz at 500 and 125.1 MHz for ^{1}H and ^{13}C, respectively, and 400 MHz spectrometers in $CDCl_3$. The ^{1}H and ^{13}C NMR spectra are given in the Supporting Information.

2.3 | Deuteriation

Traditionally, deuteriation has been done in two ways. If the compound is well soluble in CH_3OD, deuteriation can be done simply by dissolving the compound in a mixture of CH_3OH and CD_3OD and evaporating off the methanol under a vacuum. If the compound is less soluble in methanol, an alternative procedure is to dissolve the compound in $CDCl_3$, stir this with a mixture of H_2O and D_2O, suck off the water, and dry the $CDCl_3$ with dry sodium sulfate. In the present case, the latter method was used. Deuteriation takes place primarily at the chelate proton, but in the present case, also to some extent at the central carbon.

2.4 | Calculations

DFT calculations are done at the B3LYP/6-311++G(d,p) level of theory using the Gaussian G09W software.[14] The optimized structural information is given in Tables S1–15. Energies are given in Table 1. The SCRF-PCM method[15] was applied to take account of solvent effects due to $CDCl_3$. The experimental and calculated NMR nuclear shieldings, using the GIAO method,[16,17] are shown in Tables 2, 3a, 3b, and 3c.

TABLE 1 The O ... O distances (R), and the relative energies (ΔE), Gibbs free energies (ΔG), zero point energy, and corrected solvation energies (ΔGc) for **nPM** forms with respect to the most stable form, calculated at the B3LYP/6-311++G(d,p) level of theory. Solvent $CHCl_3$.

	2PM-2A	2PM-2G	2PM-4A	2PM-4G	2PM-diketo	3PM-2A
R	2.544	2.533	2.536	2.544	...	2.530
ΔE	0.0	4.1	0.7	4.2	4.2	0.0
ΔE_{ZPE}	0.0	4.0	0.4	3.9	...	0.0
D.A[a]	−180	149	−180	−153	...	−165
D.M[b]	3.49	6.56	4.34	6.85	5.17	1.51
ΔG	0.17	4.33	0.00	2.85	2.64	0.12
ΔG_{ne}	0.03	0.16	0.00	0.10	−0.04	0.04
ΔG_C	0.14	4.17	0.00	2.75	2.68	0.08

Note: ΔE: relative energy related to the most stable form of each molecule, in kcal/mol; ΔE_{ZPE}: the relative energy by considering zero point energy, in kcal/mol. ΔG_{ne} is non-electrostatic terms in kcal/mol; ΔG in kcal/mol; ΔG_C are the corrected solvation energies in kcal/mol. The populations in chloroform: **2PM**: (2PM-2A: 42.7%, 2PM-2G: 0.04%, 2PM-4A: 56.8%, 2PM-4G:0.45%, 2PM-4GHB:0.005%). **3PM**: (3PM-2A: 29.7%, 3PM-2G: 14.5%, 3PM-4A: 36.15%, and 3PM-4G: 19.6%) **4PM**: (4PM-2: 34.4% and 4PM-4: 65.6%).

[a]D.A dihedral angle.

[b]D.M dipole moment in Debye.

TABLE 1 (Continued)

	3PM-2G	3PM-4A	3PM-4G	3PM-diketo	4PM-2	4PM-4	4PM-diketo
R	2.530	2.524	2.526	...	2.533	2.532	...
ΔE	0.4	0.8	1.1	4.9	0.0	0.5	4.7
ΔE_{ZPE}	0.3	0.6	0.7	...	0.0	0.2	...
D.A[a]	162	163	163	...	163	−165	...
D.M[b]	6.22	1.72	5.96	3.03	4.28	3.52	4.52
ΔG	0.54	0.00	0.36	3.41	0.38	0.00	3.28
ΔG_{ne}	0.06	0.00	0.02	−0.18	0.03	0.00	−0.12
ΔG_C	0.48	0.00	0.34	3.59	0.35	0.00	3.40

Note: ΔE: relative energy related to the most stable form of each molecule, in kcal/mol; ΔE_{ZPE}: the relative energy by considering zero point energy, in kcal/mol. ΔG_{ne} is non-electrostatic terms in kcal/mol; ΔG in kcal/mol; ΔG_C are the corrected solvation energies in kcal/mol. The populations in chloroform: **2PM**: (2PM-2A: 42.7%, 2PM-2G: 0.04%, 2PM-4A: 56.8%, 2PM-4G:0.45%, 2PM-4GHB:0.005%). **3PM**: (3PM-2A: 29.7%, 3PM-2G: 14.5%, 3PM-4A: 36.15%, and 3PM-4G: 19.6%) **4PM**: (4PM-2: 34.4% and 4PM-4: 65.6%).

[a]D.A dihedral angle.

[b]D.M dipole moment in Debye.

TABLE 2 The experimental ^{13}C chemical shifts of the keto–enol forms.[a]

Carbon	2PM	3PM	4PM
C-1′	152.5	130.7	141.9
C-2′	-	148.3	120.3
C-3′	149.6	-	150.7
C-4′	122.5	154.0	-
C-5′	137.4	123.8	150.7
C-6′	126.6	134.5	120.3
CH_3	26.5	25.9	26.8
C-1	181.1	181.0	178.6
C-2	97.6	97.1	98.1
C-3	195.4	194.4	197.0

[a]The numberings according to Figure 1a.

3 | RESULTS AND DISCUSSION

3.1 | Calculations

Energies are calculated at the B3LYP/6-311++G(d,p) level of theory (see Table 1) to estimate the rotational properties and to evaluate the tautomerism of keto–enol-forms.

3.2 | ^{1}H NMR

The chemical shifts of the chelate OH protons are 15.67, 15.97, and 15.72 ppm for **2PM**, **3PM**, and **4PM**, respectively. These values are slightly smaller than that of benzoylacetone, 16.27 ppm.[18]

TABLE 3a Calculated ^{13}C and ^{1}H nuclear shieldings for keto–enol- and diketo-forms of 2PM.

Carbon	2PM-A	2PM-2G	2PM-4A	2PM-4G	Avg. nuclear shielding[a]	Exp.	2PM-diketo	Exp. diketo
C-6′	50.9	52.4	51.6	52.5	51.2	126.6	55.1	127.5
C-5′	40.7	41.1	40.5	41.0	40.6	137.4	40. 1	137.4
C-4′	55.1	54.4	55.5	54. 7	55.3	122.5	49.5	122.5
C-3′	28.1	26.3	27.6	26.6	27.8	149.6	27.8	149.6
C-1′	23.1	19.7	25.3	23.2	24.1	152.5	25.2	152.5
CH_3	160.1	159. 8	152.3	159. 8	156.3	26.5	150.4	31.0
C-1	−14.2	−8.4	4.3	−16. 8	−5.2	181.1	−23.3	203.0
C-2	84.2	80.9	82. 6	80.9	83.4	97.6	126.0	53.2
C-3	−8.2	−16. 8	−27.8	−8.4	−17.7	195.4	−32.0	196.1
OH	16.77	16.45	16.75	16.45	16.76	15.65	...	...
Ha1	24.68	25.76	24.71	25.76	24.70	6.81	26.95	4.37
Ha2	...	...	...	...	...	...	28.71	4.23
H-C6′	23.28	24.04	23.50	24.04	23.39	8.02	23.46	...
H-C3′	23.03	23.90	23.05	22.91	23.04	8.65	23.06	...
H-C5′	23.87	22.91	23.89	23.90	23.88	7.78	23.856	...
H-C4′	24.30	24.37	24.36	24.37	24.33	7.38	24.24	7.45
$H(H_3C)$	30.03	30.10	30.07	30.10	30.05	2.22	30.03	2.33
$H(H_3C)$	29.67	29.62	29.40	29.62	29.54	2.22	29.33	2.33
$H(H_3C)$	29.67	29.62	29.40	29.62	29.54	2.22	28.99	2.33

[a]According to the populations given in Table 1.

TABLE 3b Calculated ^{13}C and ^{1}H nuclear shieldings for keto–enol and diketo-form of 3PM.

Carbon	3PM-2A	3PM-2G	3PM-4A	3PM-4G	Avg. nuclear shielding[a]	Exp.	3PM-diketo
C-6′	41.5	42.9	42.6	44.1	42.4	134.5	38.6
C-5′	54.2	55.4	54.3	55.1	54.4	123.8	55.0
C-4′	22.9	23.0	23.7	23.3	23.4	154.0	22.2
C-2′	27.7	26.1	29.2	27.5	28.3	148.3	25.6
C-1′	45.5	45.5	48.2	48.4	47.2	130.7	46.9
CH3	159.9	159.8	153.0	153.1	155.6	25.9	152.8
C-1	−12.7	−14.1	3.7	2.6	−2.7	181.0	−16.5
C2	84.1	83.7	83.3	83.0	83.5	97.1	120.8
C-3	−8.6	−8.4	−26.7	−26.3	−19.8	194.4	−28.9
OH	16.51	16.48	16.41	16.50	16.45	15.95	...
Ha1	25.48	25.58	25.44	25.58	25.47	6.16	27.51
Ha2	...	...	...	...	...	...	28.03
H-C2′	22.67	22.28	22.74	22.37	22.64	9.04	22.41
H-C6′	23.10	23.72	23.29	23.75	23.30	8.13	23.10
H-C4′	22.95	22.93	23.01	22.95	22.97	8.70	22.89
H-C5′	24.29	24.39	24.29	24.40	24.31	7.40	24.32
$H(H_3C)$	30.05	30.08	30.01	30.00	30.02	2.19	30.12
$H(H_3C)$	29.62	29.62	29.35	29.52	29.47	2.19	29.05
$H(H_3C)$	29.62	29.62	29.48	29.39	29.512	2.19	29.60

[a]According to the populations given in Table 1.

TABLE 3c Calculated ^{13}C and ^{1}H nuclear shieldings for keto–enol and diketo-forms of 4PM.

Carbon	4PM-2	4PM-4	Avg. nuclear shielding[a]	Exp.	4PM-diketo
C-3′, C-5′	25.8	26.0	25.9	150.7	25.1
C-2′, C-6′	57.3	58.1	57.7	120.3	58.0
C-1′	34.1	36.4	35.2	141.9	36.5
CH_3	159.8	152.5	156.1	26.8	150.2
C-1	−9.6	4.2	−2.7	178.6	−22. 6
C-2	83.8	82.4	83.1	98.1	126.6
C-3	−13.3	−27.3	−20.3	197.0	−32.8
OH	16.50	16.66	16.61	15.73	...
Ha1	25.47	25.42	25.44	6.22	27.49
Ha2	...	...	...	...	28.08
H-C2′	23.61	23.75	23.70	7.69	24.19
H-C6′	24.17	24.22	24.20	7.69	23.74
H-C3′	22.85	22.86	22.86	8.75	22.82
H-C5′	22.95	23.02	23.00	8.75	22.79
H(H_3C)	30.04	29.99	30.01	2.25	29.88
H(H_3C)	29.60	29.41	29.48	2.25	29.63
H(H_3C)	29.59	29.35	29.43	2.25	29.17

[a]According to the populations given in Table 1.

3.3 | Assignment of ^{13}C NMR spectra

The ^{13}C chemical shifts of the C=O group next to CH_3 or next to a phenyl group are approximately 10 ppm apart with the higher chemical shift for the former. As the equilibrium constants are close to 1 for all three compounds, the C=O carbons can safely be assigned. The assignment of the ^{13}C resonances of the pyridine rings can be done based on a comparison of **4PM** with pyridine to obtain the effect of the C = ... substituent. The effects at 4′ clearly cannot be obtained, but this is not a problem. The substituent effects can be used together with pyridine chemical shifts to assign the resonances of **2PM** and **3PM**. The assignments are given in Tables 2, 3a, 3b, and 3c are plotted vs. the calculated nuclear shielding as seen in Figure 3. A very good agreement is obtained; see Section 3.4.

3.4 | Correlations

^{1}H and ^{13}C chemical shifts in the keto–enol system may be calculated by correlating with the calculated nuclear shieldings, as seen in Figure 3a,b and Tables 3a, 3b, and 3c. The averaged nuclear shieldings are obtained by averaging using the calculated populations (Table 1) and nuclear shieldings given in Tables 3a, 3b, and 3c. Taking both populations of tautomeric and conformational forms into account (see Tables 3a, 3b, and 3c), very good correlations are obtained:

$$^{13}C: \delta C = -0.9625\,\sigma C + 176.37 \quad R^2 = 0.9997.$$

$$^{1}H: \delta H = -1.0411\,\sigma H + 32.764 \quad R^2 = 0.9963.$$

3.5 | Deuterium isotope effects on ^{13}C chemical shifts

3.5.1 | Keto–enol-forms

For **2PM** the two-bond deuterium isotope effects due to deuteriation at the chelate proton at C-1 and C-3 are very similar, C-3 = 0.61 ppm and C-1 = 0.62 ppm. The effect due to deuteriation at C-2 is 0.1 ppm at C-3, whereas the one-bond deuterium isotope effect at C-2 is 0.24 ppm. For **3PM**, the effects at C-1 and C-3 are 0.57 ppm and 0.55 ppm, respectively, whereas a small effect, 0.01 ppm, is seen at C-1′. The one-bond effect due to deuteriation at C-2 is 0.27 ppm. For **4PM**, the picture is different. The two-bond deuterium isotope effect at C-1 is 0.79 ppm, whereas that at C-3 is only 0.45 ppm. A small effect, 0.01 ppm, is found at C-1′. The one-bond-deuterium effect at C-2 is 0.26 ppm.

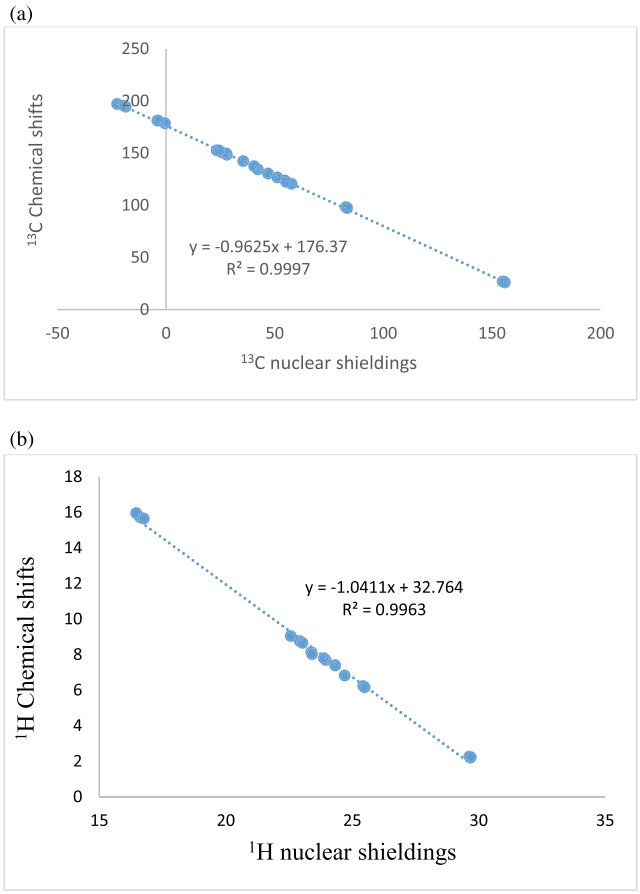

FIGURE 3 (a) Plot of the experimental ^{13}C chemical shifts for keto–enol-forms versus averaged calculated nuclear shieldings. (b) Plot of the experimental ^{1}H chemical shifts for keto–enol-forms versus averaged calculated nuclear shieldings.

For **2PM** and **4PM,** the average two-bond deuterium isotope effects are 0.62 ppm, whereas the average in the case of **3PM** is only 0.56 ppm, indicating that the hydrogen bond is slightly weaker in the latter.

3.5.2 | Diketo-forms

In the case of the diketo form of **2PM**, the one-bond isotope effect due to deuteriation at C-2 is 0.28 ppm.

3.6 | Structures and conformations

As seen from the NMR spectra, the keto–enol forms are clearly preferred. Only for **2PM,** a diketo form is observed (12%).

The nitrogens of the pyridine rings of **2PM** and **3PM** may be gauche (**G**) or anti (**A**) to the oxygen at C-1 (see Figure 2). As seen in Table 1, for **2PM** the anti-conformation (**A**) is clearly preferred for both keto–enol forms. In the case of **2PM,** the form with a hydrogen bond to the pyridine nitrogen **2PM-4GHB** is also a possibility (see Figure 2). The form with the C=O being parallel to the C-1-O bond is not shown. This has slightly higher energy. However, none of these forms play a role, as they are slightly populated (see Table 1). Both the fact that the OH ... O hydrogen bond is lost and the repulsion between nitrogen of the ring and the C-1-O bond is against this type of hydrogen bonding. For **3PM,** the anti-conformations are still preferred but not heavily.

The calculations show that for **2PM-2A** and **2PM-4A,** the pyridine ring is in the hydrogen bond ring plane, whereas in all other cases, it is slightly twisted out of the ring plane (Table 1). This can be explained by a weak attraction between the ring nitrogen and CH-2 and the absence of a steric interaction between the H-6′of the pyridine ring and CH-2. In the case of **2PM-2A** and **2PM-4A**, this is also clearly reflected in the chemical shifts of H-2, which is 6.81 ppm for **2PM** and 6.19 ppm for **3PM** and **4PM**.

3.7 | Equilibria

In an equilibrium system, the isotope effects on ^{13}C chemical shifts are described by two contributions, the intrinsic (int) and the equilibrium part (the first term) as seen in Equation (1):

$$\Delta C-1 = \Delta x\,(\delta C-1-\delta C-3)+x^2\Delta C-1(OD)_{int} + (1-x)^4\Delta C-3(OD)_{int}. \quad (1)$$

x is mole fraction. Δx is the change in the mole fraction upon deuteriation. δC-y is chemical shifts.

It is obvious for **2PM** and **3PM** that the isotope effects at C-1 and C-3 are very similar, which means that the equilibrium constant must be close to 1. For **4PM,** the two-bond deuterium isotope effects at C-1 and C-3 are different. The keto–enol equilibrium constant can be estimated from the graph of fig. 5 of Bolvig and Hansen,[19] K = 1.2. The mentioned equilibrium constants can be compared with their calculated values at B3LYP/6–311++G (d,p) in $CHCl_3$ as a solvent, 1.33, 1.22, and 1.91 for **2PM, 3PM,** and **4PM**, respectively.

The keto–enol equilibrium constant of benzoylacetone is 1.3 (OH-form close to the phenyl ring is dominant).[20] This was also found in the present case for **4PM,** and in the case of **4N**-pyridoyl-benzoylmethane, K = 2.3.[2] However, for **2N**- and **3N**-pyridoyl-benzoylmethane, the situation is the opposite; K is less than one. In the present case, **2PM** and **3PM** showed an

equilibrium constant close to 1. In other words, nitrogen in the 2 or 3 positions of the pyridine ring promotes the tautomer with OH on the "C=O" carbon away from the pyridine ring (4-type, see Figure 2).

4 | CONCLUSIONS

The conformations and the tautomerism of the **nPM**s have been elucidated by means of DFT calculations, and only in the case of **2PM** is the pyridine ring coplanar with the hydrogen bond system due to positive interactions between H-2 and the nitrogen, as also revealed by the ^{1}H chemical shifts.

Considering that the keto–enol equilibrium constant for benzoylacetone is 1.3, the nitrogen in the 4-position of the pyridine ring has little effect, whereas those in the 2- and 3-position have, as the equilibrium constants are close to one in these compounds.

In contrast to benzoylacetone and other heterocycloylacetones, only for **2PM,** a keto-form is seen in the NMR spectra.

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