An experimental (flash vacuum pyrolysis) and theoretical study of the tautomerism of pyrazolinones at high temperatures

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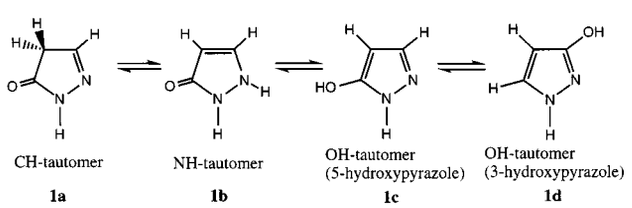
Flash vacuum pyrolysis experiments were carried out between 500 and 800 °C on 3(5)-phenyl- and 3(5)-methyl-pyrazolinones and on 3(5)-methoxy-5(3)-phenylpyrazole. The origin of the isolated products (mainly indanone, hydroxyalkynes and α,β-unsaturated aldehydes) can be explained as arising from the hydroxy tautomers of pyrazolinones. Temperature effects on the tautomeric equilibrium of 1-phenyl-3-methylpyrazolinone in solution show that the percentage of the CH tautomer increases with the temperature. MP2 *ab initio* calculations on the model compound, pyrazolinone itself, have been used to rationalize these findings. The problem of the aromaticity of the four tautomers of pyrazolinone has been examined through Schleyer's NICS (nuclear independent chemical shifts) calculations.

Introduction

For several years we have been interested in the flash vacuum pyrolysis (FVP) of pyrazoles and indazoles (benzopyrazoles).[1–7] Pyrazolinones have four tautomers, two of which, **1c** and **1d**, are 5- and 3-hydroxypyrazole derivatives:[8]



Scheme 1

As a natural extension of our work, we decided to subject some pyrazolinones to FVP and to calculate theoretically the effect of the temperature on the equilibria between the above represented tautomers of **1**. In addition, we determined experimentally the variation of K_T with the temperature by ^{1}H NMR in solution for a model compound.

Experimental and theoretical methods

Experimental procedures

Synthesis of pyrazolinones. 3-Methylpyrazolinone (**4**) and 1-phenyl-3-methylpyrazolinone (**5**) are commercially available (Aldrich). 3-Phenylpyrazolinone (**2**) was prepared by reaction between benzoylacetanilide and hydrazine hydrate (20% excess) in ethanol.[9a] Yield 82%, mp 241–242 °C, lit. 239–242 °C.[10] *m/z* (30 eV): 160 (M^+). 3(5)-Methoxy-5(3)-phenylpyrazole (**3**) was prepared by methylation of **2** by diazomethane in diethyl ether, following the technique described by Vogel.[9b] Yield 55%, mp 109–110 °C, lit. 106–106.5 °C.[11] *m/z* (30 eV): 174 (M^+).

FVP. The experiments were carried out in flash vacuum pyrolysis equipment, using a GAYNOR PRDH temperature controller and a Thermolyne (21100) tube furnace. Oxygen free dry nitrogen was used as carrier gas. ^{1}H NMR spectra were recorded with a Bruker 200FT spectrometer and are expressed in δ, downfield from TMS. Mass spectra were determined with a Finnigan 3300 spectrometer. The products formed by pyrolysis were identified by comparison (^{1}H NMR, MS) with authentic samples.

Product identification. Indanone (**6**):[12] mp 42–43 °C. δ_H(DMSO-d_6): 2.85 (2H, t), 3.51 (2H, t), 7.50–7.70 (4H, m). 1-Phenyl-3-hydroxyprop-1-yne (**7**):[13] δ_H(DMSO-d_6): 3.25 (1H, s), 4.35 (2H, d), 7.50–7.75 (5H, m). *trans*-Cinnamaldehyde (**8**):[14] δ_H(DMSO-d_6): 6.85 (1H, dd), 7.65–7.85 (6H, m), 10.50 (1H, d). *cis*-Cinnamaldehyde (**9**).[15] δ_H(DMSO-d_6): 6.43 (1H, dd), 7.65–7.80 (6H, m), 10.60 (1H, d). 1-Hydroxybut-2-yne (**10**):[16] δ_H(DMSO-d_6): 2.07 (3H, s), 3.25 (1H, s), 4.46 (2H, d). *trans*-Crotonaldehyde (**11**):[17] δ_H(DMSO-d_6): 2.19 (3H, d), 6.21 (1H, m), 6.82 (1H, m), 10.05 (1H, d). *cis*-Crotonaldehyde (**12**):[18] δ_H(DMSO-d_6): 2.35 (3H, d), 6.51 (1H, m), 6.95 (1H, m), 10.50 (1H, d).

NMR analysis. ^{1}H NMR spectra at different temperatures were recorded in a Varian Inova 400 spectrometer working at 400 MHz. Compound **5** was dissolved in CD_3OD (0.096 mol L^{-1}) and the percentages of CH and (NH + OH) tautomers determined by repeated integration of the methyl signals to determine K_T (defined as [CH]/[NH + OH]); the range of temperatures used was 213–296.8 K. Similar experiments were carried out in DMSO-d_6 for a range of temperatures between 294 and 363 K; in this case the percentages were determined on the aromatic proton signals of phenyl groups. The results are reported in Table 2.

Calculations

All the *ab initio* optimizations and frequency calculations have been performed using the Gaussian-94 program.[19] All the structures have been fully optimized with the 6-31G** basis set[20] using the MP2 level.[21] The stationary points found were characterized as minima by frequency calculations at MP2/6-31G** level (all frequencies being real). The zero-point vibrational energy (ZPE) has been calculated for all the tautomers studied. *Ab initio* calculations have been carried out considering a fixed temperature of 298.15 K and a fixed pressure of 1.0 atm. These calculations (including frequency calculations) provide

Table 1 Results of the FVP experiments (in percentage)

Starting material	*T*/°C	Starting material	Indanone (**6**)	Hydroxyalkynes	α,β-Unsaturated aldehydes	Other compounds
3(5)-Phenylpyrazolin-5(3)-one (**2**)	600	48 (**2**)	18 (**6**)	11 (**7**)	19 (**8** + **9**)	—
	700	0 (**2**)	30 (**2**)	20 (**7**)	33 (**8** + **9**)	—
3(5)-Methoxy-5(3)-phenylpyrazole (**3**)	500	86 (**3**)	—	—	—	14 (**2**)
	600	65 (**3**)	2 (**6**)	10 (**7**)	2 (**8** + **9**)	20 (**2**)
	700	—	8 (**6**)	13 (**7**)	60 (**8** + **9**)	10 (**2**) + 9 (styrene)
	800	—	20 (**6**)	19 (**7**)	20 (**8** + **9**)	41 (styrene)
3(5)-Methylpyrazolin-5(3)-one (**4**)	600	55 (**4**)	—	14 (**10**)	29 (**11** + **12**)	—
	700	—	—	28 (**10**)	71 (**11** + **12**)	—

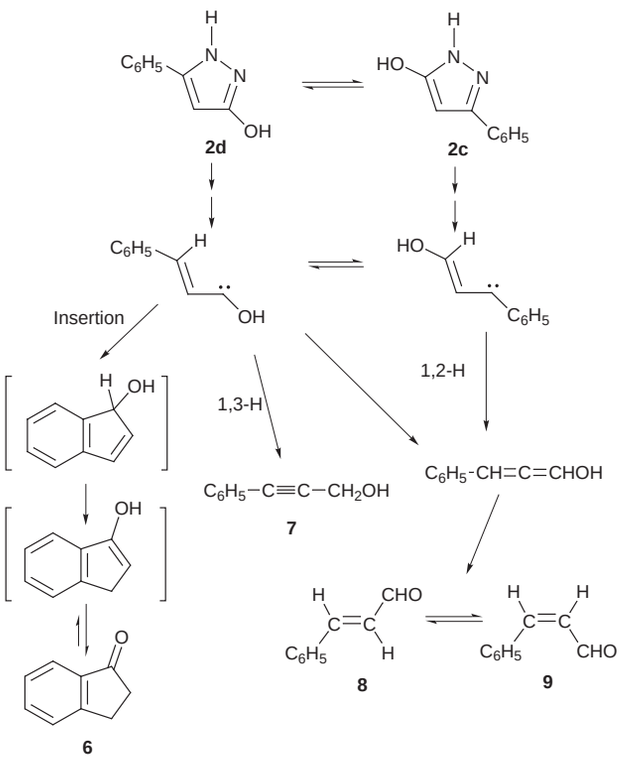


Fig. 1 Proposed pathway for the FVP of pyrazolinone **2**.

the total energy of the molecule (*E*, in a.u.) taking into account all the corrections (included the thermal and ZPE corrections) and the entropy (*S*, in cal mol^{-1} K^{-1}).† Assuming that these corrected energy values are equal to the enthalpy (ΔE + ΔZPE + Δtherm, in kcal mol^{-1}) and using eqn. (1) it was

$$\Delta G = (\Delta E + \Delta\mathrm{ZPE} + \Delta\mathrm{therm}) - T\Delta S \qquad (1)$$

possible to evaluate the difference in Gibbs energy between tautomers (ΔG, in kcal mol^{-1}) at a certain temperature.

By using these ΔG values and eqn. (2) it was possible to

$$\Delta G = -RT \ln K \qquad (2)$$

determine the constants (*K*) for each tautomeric equilibrium at a certain temperature, and therefore, the corresponding populations of each tautomer in the equilibria.

Finally, nuclear independent chemical shifts (NICS) calculations were performed to estimate the aromaticity of pyrazolinone tautomers. This needs first to determine the ring critical points,[22] then the chemical shifts at these points using the GIAO (gauge including atomic orbitals) method.[23]

† 1 cal = 4.184 J.

Results and discussion

1. FVP experiments with compounds 2–4

Compound **2** was pyrolysed between 600 and 700 °C. The identified products were indanone **6**, **7**, **8** and **9** (Table 1 and Fig. 1). Analysis of the reaction products (**6**–**9**) suggests that the general mechanism for nitrogen extrusion of pyrazoles[7] may be applicable. In this mechanism, a vinylcarbene (hereinafter, **v.c.**) is formed as depicted in Fig. 1.

Compound **2** reacts as a mixture of **2c** and **2d** or from any of them if the equilibrium between **v.c.**s is fast enough. Tautomer **2c** is not necessary to explain the origin of the identified products. If the dominant tautomer were a pyrazolinone **a** or a pyrazolone **b**, compounds resulting from the extrusion of CO would be expected.[24] Therefore, all the products **6**–**9** result from the rearrangement of the **v.c.**s. The **v.c.** formed from **2d** undergoes an aromatic C–H insertion to yield a hydroxyindene, which tautomerizes to **6**, and a 1,3-hydrogen migration to yield **7**. A 1,2-hydrogen migration from any (or from both) **v.c.**s yields a cumulene which tautomerizes to **8** and **9**. Styrene (**10**) is also found in these experiments. This compound could be formed from cinnamaldehyde by a radical reaction.[25] The presence of radicals was confirmed by carrying out the reaction with toluene as carrier gas; in these conditions bibenzyl was isolated. In summary, of the four possible tautomers of 3(5)-phenylpyrazolinone (**2**), only the 3-hydroxy-5-phenylpyrazole (**2d**) is necessary to explain the observed products, although the presence of **2c** cannot be excluded. The possibility that all the products came from **2c**, through an isomerization of the corresponding **v.c.** is less probable.

The FVP of 3(5)-methoxy-5(3)-phenylpyrazole (**3**) (Table 1) gives very similar results. At low temperatures, the formation of 3(5)-phenylpyrazolinone (**2**) resulting from the loss of the methyl group is observed. This reaction occurs by a radical mechanism (formation of bibenzyl when toluene was used as a carrier). This reaction has precedents in the thermolysis of alkoxybenzene which results mainly in the formation of phenol.[26] At higher temperatures the main product is **10** formed from cinnamaldehyde by a radical mechanism as in the reactions of **2**.[25] In summary, the loss of a methyl group from **3** requires less energy than the nitrogen extrusion preventing the formation of the corresponding **v.c.**s. This result favours the conclusion that only the hydroxy tautomers are the reactive species in phenylpyrazolinones, methoxypyrazoles being only precursors of these tautomers.

The last example concerns 3-methylpyrazolinone (**4**). In this case (Table 1 and Fig. 2) we have identified 1-hydroxybut-2-yne (**11**), *trans*-crotonaldehyde (**12**) and *cis*-crotonaldehyde (**13**). This result is very similar to the preceding pyrazolinone **2** and could be explained, through the corresponding **v.c.**s and cumulene, starting from pure 3-hydroxy-5-methylpyrazole (**4d**) or from both hydroxy tautomers, **4d** and **4c**. The possibility that all the compounds resulted from **4c** cannot be ruled out, although it is a less probable explanation.

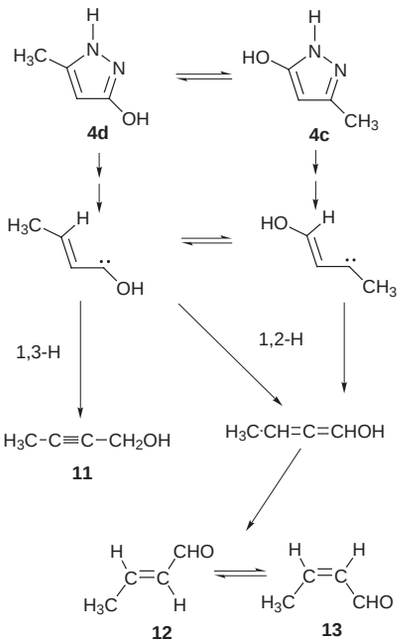
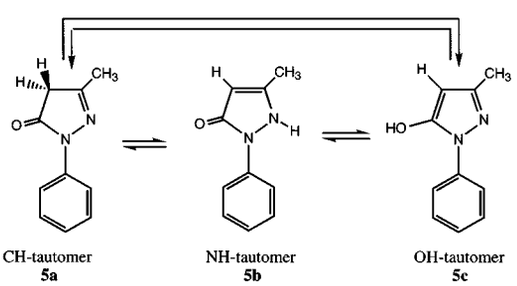


Fig. 2 Proposed pathway for the FVP of pyrazolinone **4**.

2. Variable temperature ^{1}H NMR of compound 5 in solution

Surprisingly enough there are very few studies of the effect of the temperature on the prototropic equilibria of pyrazolinones. In a classical book of 1976,[8] there is only one reference and it concerns 1-phenyl-3-acetylamino-2-pyrazolin-5-one (**14**).[27] For this compound in DMSO (by ^{1}H NMR) rough values are given for the equilibrium between **14a** and **14b**, $\Delta H \sim 3$ kcal mol^{-1} and $\Delta S \sim 7$ cal mol^{-1} K^{-1}. An examination of the old spectra and a new treatment of the data lead to values of $\Delta H = 2.5$ kcal mol^{-1} and $\Delta S = 5.8$ cal mol^{-1} K^{-1}. Since nothing more recent has been published,[8] we decided to carry out similar experiments on 1-phenyl-3-methyl-2-pyrazolin-5-one (**5**), probably the most studied pyrazolinone.[8] Because in the ^{1}H NMR time-scale, tautomers **b** and **c** interconvert very rapidly, the determination by NMR refers to the equilibrium between the CH tautomer (**5a**) and a mixture, in unknown proportions, of tautomers NH (**5b**) and OH (**5c**).



Scheme 2

The results we obtained are reported in Table 2. To analyse together results in methanol and in DMSO we assumed that the solvent effect is independent of the temperature (there is more CH tautomer **5a** in DMSO than in methanol). This allowed us to treat the eight experiments with only one equation. The results are: solvent effect, $\Delta\Delta H = (0.15 \pm 0.01)$ kcal mol^{-1}, $\Delta H = (2.1 \pm 0.05)$ kcal mol^{-1}, $\Delta S = (4.0 \pm 0.2)$ cal mol^{-1} K^{-1} (for $n = 8$ and $r^2 = 0.998$). Therefore, this study shows that the only tautomers present at 0 K are either the NH or the OH ones.

3. Theoretical calculations of compound 1

This compound, the simplest (but one of the most difficult to synthesize) of all pyrazolinones, has been the subject of several

Table 2 Variation of the percentages of CH **a** and NH + OH **b** + **c** tautomers with the temperature (compound **5**)

T/K	Solvent	% **5a**	% (**5b** + **5c**)	K_{eq}
213	Methanol-d$_4$	3.8	96.2	0.0395
230	Methanol-d$_4$	5.1	94.9	0.0537
267	Methanol-d$_4$	9.7	90.3	0.1074
298.6	Methanol-d$_4$	14.4	85.6	0.1682
294	DMSO-d$_6$	17.2	82.8	0.2077
303	DMSO-d$_6$	18.8	81.2	0.2315
333	DMSO-d$_6$	24.2	75.8	0.3193
363	DMSO-d$_6$	29.4	70.6	0.4164

ab initio studies in recent years. The first one, by Hillier *et al.*[28] used 3-21G optimized geometries of the four tautomers, **1a**–**1d** (for **1a** and **1b** the optimization was carried out at the 6-31G** level) and on those geometries MP2, MP3 and MP4SDTQ calculations were carried out as well as solute–solvent interactions. In the gas phase (which mainly interests us in the present context), the most stable tautomer is **1a** except for MP2-6-31G**//3-21G calculations, which favours tautomer **1d**.[28] Shortly after, Cao, Schäfer *et al.*[29] included in the set some very unimportant tautomers and two conformations of the OH for the 3-hydroxy tautomer **1d** and extended considerably the level of the calculations [CCSD//6-311+G(3df,2p)]. Their conclusion is that in the gas phase the most stable tautomer is **1d** with the H of the OH pointing to the nitrogen atom (**1d′**). Recently, Luque *et al.*[30] confirm the conclusions of Schäfer *et al.* and develop the part concerning solvent effects. The same year, Sakurai *et al.*[31] reported calculations on 1,3-dimethyl-2-pyrazolin-5-one which, lacking a tautomer of type **d**, resulted in the type **a** tautomer being the most stable. We ourselves have studied theoretically the more complex case of 1-(2′,4′-dinitrophenyl)pyrazolinones.[32]

It appears that the problem was already quite well understood but we wanted to know the effect of the temperature on the equilibria since the FVP experiments were carried out in the gas phase between 500 and 800 °C. For that reason, we performed MP2/6-31G** *ab initio* calculations which provided the total energy of the four tautomers (**1a**, **1b**, **1c** and **1d′**). It had been already discussed[29] that the use of MP2 optimized geometries in these particular tautomers was necessary to obtain accurate results in terms of relative stability. The four structures optimized at that level are represented in Fig. 3. Also, the frequencies were computed providing the thermal and zero-point vibrational energy (ZPE) corrections, and the entropies. The relative Gibbs energy ($\Delta\Delta G$) was then calculated by using eqn. (1) with the entropies obtained and with the corrected energies (ΔE + ΔZPE + Δtherm).

The results (see Table 3) show that tautomer **1d′** is the most stable of all of them in the gas phase and at a temperature of 298.15 K, in agreement with the results obtained by Cao and Schäfer.[29] Then, making the asumption that enthalpy and entropy were independent of temperature and by using again eqn. (1), the relative free energies of these tautomers at different temperatures (100, 298.15, 400, 500, 750 and 1000 K) were calculated (see Table 3). Thus, the equilibrium constants K were deduced by using eqn. (2) and the relative populations of the four tautomers were obtained and plotted together in Fig. 4. It can be observed that the population of the most stable (**1d′**) decreases when the temperature increases whereas the other three tautomers, less stable than **1d′**, increase their populations with temperature except for tautomer **1b**, which remains almost nonexistent. This behaviour can be explained if one considers that the difference in entropy between tautomers **1b**/**1d′** is negative ($\Delta S = -0.0008$ kcal mol^{-1} K^{-1}). This value, which in principle could be considered as part of the error of the calculation, was checked by performing B3LYP/6-31G** calculations over both tautomers which also provided a negative value ($\Delta S = -0.0006$ kcal mol^{-1} K^{-1}). It is known that

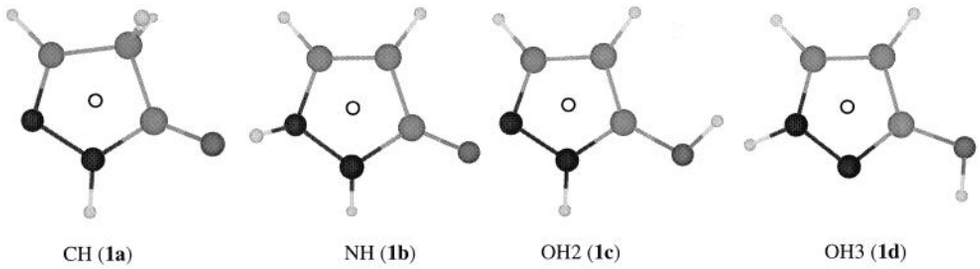
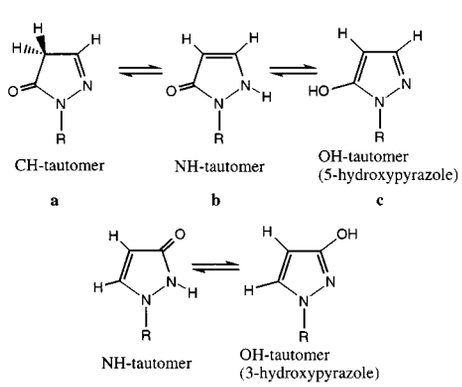


Fig. 3 Structures of the four tautomers studied (**1a**, **1b**, **1c** and **1d′**) optimized at the MP2/6-31G* level. The ring critical points calculated using Bader's theory are represented by an empty circle.

Table 3 Total energies (E_T, au), zero-point energies (ZPVE, kcal mol^{-1}), thermal corrections (Therm, kcal mol^{-1}), entropies (S, kcal mol^{-1} K^{-1}), corrected relative energies (ΔE, kcal mol^{-1}), relative free energies at different temperatures [$\Delta\Delta G(T)$, kcal mol^{-1} (K)] and equilibrium constants (K) calculated at the MP2/6-31G** level for the four tautomers studied

	1a	**1b**	**1c**	**1d′**
E_T	−300.5705424	−300.5584301	−300.5681505	−300.5739636
ZPVE	47.49255	48.37284	47.89662	48.04952
Therm	50.623	51.276	51.101	51.125
S	0.072318	0.070270	0.072155	0.071067
ΔE	1.09	10.22	3.47	0.0
$\Delta\Delta G(100)$	0.96	10.30	3.36	0.0
$\Delta\Delta G(298.15)$	0.72	10.46	3.15	0.0
$\Delta\Delta G(400)$	0.59	10.54	3.03	0.0
$\Delta\Delta G(500)$	0.46	10.62	2.93	0.0
$\Delta\Delta G(750)$	0.15	10.82	2.65	0.0
$\Delta\Delta G(1000)$	−0.16	11.02	2.38	0.0
$K(100)$	0.01	0.0	0.0	
$K(298.15)$	0.30	0.0	0.01	
$K(400)$	0.47	0.0	0.02	
$K(500)$	0.63	0.0	0.05	
$K(750)$	0.90	0.0	0.17	
$K(1000)$	1.08	0.0	0.30	



Scheme 3

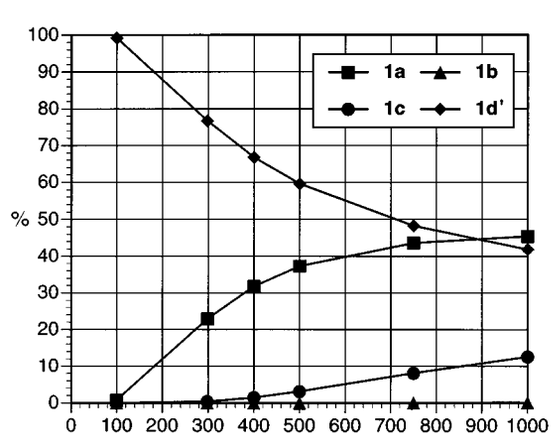


Fig. 4 Evolution of the populations of **1a**, **1b**, **1c** and **1d′** tautomers with temperature.

B3LYP calculations provide much more accurate frequencies than MP2 and, therefore, it will supply more accurate entropy values.[33]

4. Comparison of theoretical calculations with FVP and ^{1}H NMR experiments

Since most studies carried out with pyrazolinones concern N(1)-substituted derivatives, it is convenient to consider two different equilibria, one between **a/b/c** characteristic of 1-R-pyrazolin-5-ones and another between **b/d** characteristic of 1-R-3-hydroxypyrazoles. In ref. 8, it is stated that studies in the vapour phase are rare, nevertheless it is reported that the presence of a ν(C=O) band at 1720 cm^{-1} in the IR spectrum of the 1-phenyl-3-methylpyrazolin-5-one (**5**) indicates that it exists in the vapour as the CH form (**5a**).[34,35] On the other hand, it is clearly established that 3-hydroxypyrazoles exist as such, **d**, in all experimental conditions.

According to our theoretical calculations, the order of stability at 298.15 K is **1d′ > 1a > 1c ≫ 1b**. This agrees with the experimental evidence we have just summarized (**a > c + b** and **d > b**). Increasing the temperature tends to equalize the populations and at 890 K, the stabilities of **1d′** and **1a** become identical (see Fig. 4). At higher temperatures (remember that the FVP experiments were carried out between 500 and 800 °C, *i.e.* 750–1000 K), the CH tautomer becomes the most stable, although at 1000 K it is only 0.16 kcal mol^{-1} more stable than the 3-OH. In conclusion, the FVP results are better explained as starting from **2d** and **4d** than from mixtures of these tautomers with **2c** and **4c**. No compounds were observed resulting from **2a** and **4a**, but there is a factor that we have not considered, the rate of pyrolysis of the different tautomers. It is possible that the CH tautomers decompose more slowly than the OH ones. Regarding the fact that 3-hydroxypyrazoles always exist as **d**,

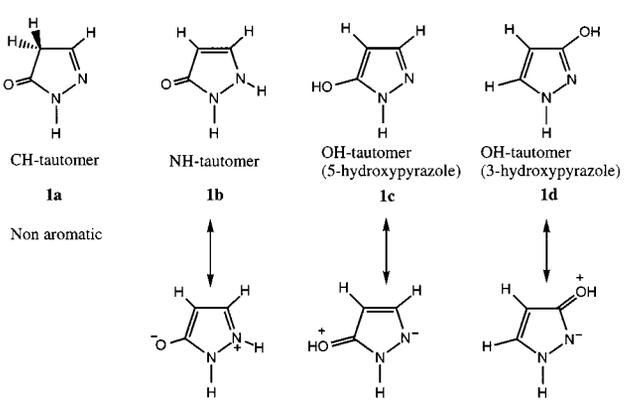
the data reported in Table 3 show that **1d′** is much more stable than **1b**.

Concerning the NMR experiments, there is an apparent contradiction between the conclusions of the calculations (only **1a** at 0 K) and those reported for **5** (only **5a** in the gas phase)[8] on one hand and those of the NMR experiments (only **5b** or **5c** at 0 K in methanol or DMSO) on the other. Obviously, the explanation should lie on solvent effects. Three publications have reported theoretical studies of solvent effects on these equilibria. According to Hillier *et al.*[28] water shifts the equilibrium towards the NH (**1b**) or the OH (**1c**) tautomers, depending on the model used. Cao, Schäffer *et al.*[29] conclude that the NH tautomer (**1b**) is the most stable in water (Luque *et al.*[30] have only examined the solvent effects on the equilibrium **1b/1d/1d′** which is not relevant for the present discussion). Ono *et al.*[31] conclude, from B3LYP/6-31G* calculations, that the CH tautomer **a** of 1,3-dimethylpyrazolin-5-one is the most stable in both the aqueous and vapour phases. This last conclusion is probably wrong since we found, also in the gas phase and B3LYP level, that **1a** was more stable than **1d′** and this is in contradiction with our MP2 results and those of Shäfer *et al.*[29] In summary, in solution, the effect of solvents like methanol and DMSO, dominates over temperature effects.

A last comment concerning the equilibrium between **1c** and **1d′**. The difference in stability between **1c** and **1d′** (3.5 kcal mol^{-1}) is very unusual for annular tautomerism of azoles where the 3-R and 5-R tautomers have similar stabilities.[36–38] The only explanation is the presence of an intramolecular hydrogen bond (IMHB) in **1d′** which stabilizes this tautomer. This HB is not present in 3(5)-methoxypyrazole which is a "bad" model for 3-hydroxypyrazole.

NICS and the aromaticity of the four tautomers

The problem of the stability of pyrazolinone tautomers is related to their aromaticity.[8,39] It was always clear that the CH tautomer is not aromatic and that the OH tautomers are aromatic, but more or less aromatic than pyrazole? The NH tautomer was considered aromatic although less than the OH ones. These qualitative reasonings were based on our ability to write down charged resonance structures, that in the case of the NH tautomer would justify its aromaticity and in the case of the OH tautomers would decrease if compared with pyrazole. We decided to employ Schleyer's approach[40] using the NICS (Nuclear Independent Chemical Shifts) values computed at the ring critical points calculated using Bader's theory[22] (see Fig. 3). To be consistent with Schleyer's data, we used HF/6-31+G* calculations to evaluate the NICS with geometries optimized at the MP2/6-31G** level and ring critical points calculated in these geometries. As a general rule negative NICS values correspond to aromatic compounds[40] and some reference NICS values, at HF/6-31+G* level, for pyrrole, thiophene and furan are −15.1, −13.6 and −12.3 ppm respectively.[40]



Scheme 4

For pyrazole itself, our computed NICS value is −14.95 ppm, which is very close to pyrrole. The OH tautomers have NICS values of −14.55 (**1c**) and −14.45 ppm (**1d′**), indicating that the OH substituent does not alter the aromaticity of pyrazole, *i.e.* that dipolar charged forms are not important. Finally, the NH tautomer (**1b**) has a NICS of −6.75 ppm, intermediate between those of the aromatic pyrazoles and that of the non-aromatic CH tautomer (**1a**, NICS = −0.25 ppm).

Supplementary information available

All the calculated geometries and ring critical points coordinates are available on simple request from one of us (I.R.: rozas@pinar1.csic.es).

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