THE TAUTOMERISM OF PYRAZOLINES (DIHYDROPYRAZOLES)

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Dedicated to Professor Josep Castells on the occasion of his 90th Birthday

ABSTRACT

The exception to the rule that Δ^3 -pyrazolines are not stable unless both nitrogen atoms are substituted that has been recently published, *Tetrahedron Lett.* **55**, 2208, (2014), has been proved false. By means of GIAO/B3LYP/6-311++G(d,p) calculations, it has been shown that the product is a pyrazole formed by rearrangement.

Keywords: pyrazolines, dihydropyrazoles, rearrangement, NMR, DFT calculations, GIAO

1. INTRODUCTION

There exists a clear imbalance in tautomeric studies of heterocycles between the much studied aromatic compounds and the seldom studied non-aromatic compounds. A clear example is the pyrazole/pyrazoline pair. There are hundreds of publications dealing with pyrazoles,^{1,2} while there is only one paper where a theoretical study of the tautomerism of pyrazolines (dihydropyrazoles) is reported.³ This is not due to the relative importance of both heterocycles, at least, not only, but more probably to the fact that pyrazole tautomers have similar energies while in the case of pyrazoline one tautomer is clearly more stable than the others. Pyrazolinones (pyrazolones) occupy an intermediate situation having both aromatic and non-aromatic tautomers, and they have been also much studied.^{1,4}

According to our calculations carried out at the B3LYP/6-311++G(d,p) level for compounds **1a-1c**,³ that we have completed for the present work for compounds **2b-2d** (Scheme 1), the Δ^2 -pyrazolines (4,5-dihydro-1*H*-pyrazoles, **1b** and **2b**) are more stable than the Δ^1 -pyrazolines (4,5-dihydro-3*H*-pyrazoles, **1a**). By far, the Δ^3 -pyrazolines (2,3-dihydro-1*H*-pyrazoles, **1c**, **2c**, **2d**) are the less stable. It is interesting to note that the methyl group stabilizes the Δ^3 tautomers.

Scheme 1. The different pyrazolines and their relative energies in kJ·mol⁻¹.

Pyrazolines tautomerize one into another by mere heating and by acid catalysis. Thus 1-unsubstituted Δ^2 -pyrazolines, like **1b**, thermally isomerizes into Δ^1 -pyrazolines, like **1a**, that lose N₂ to yield cyclopropanes.⁵ The Δ^1 to Δ^2 isomerization is also known.⁶

N₁-H or N₂-H Δ^3 -pyrazolines (**1c**, **2c**, **2d**) are so unstable that they are not isolated and transform spontaneously into Δ^2 -pyrazolines (**1b**, **2b**) and, with some exceptions, only 1,2-disubstituted Δ^3 -pyrazolines are known.

In 1970, Wittig and Hutchison,⁷ reported the following sequence of reactions (**3** → **4** → **5**, **Scheme 2**) where a N₁-H Δ^3 -pyrazoline was isolated.

We demonstrated afterwards that the product of rearrangement of the pyrazolinine **3** was not the pyrazole **4** but the isopyrazole **6** that was reduced by lithium aluminium hydride to a Δ^2 -pyrazoline **7**, therefore disproving an example of N₁-H Δ^3 -pyrazoline stable. However, we described that these compounds could be stable when they carry special substituents (Scheme 3).⁸

Scheme 2. Formation of a Δ^2 -pyrazoline **7** and not of a Δ^3 -pyrazoline **5**.

Scheme 3. The structure of a true N₁-H Δ^3 -pyrazoline.

When hexafluoroacetone azine (**8**) reacted with one alkene, compound **9** was isolated. The presence of a geminal trifluoromethyl group at position 5 prevented the isomerization of **9** to a Δ^2 -pyrazoline.⁸

The situation seemed clear until recently a counterexample was published.

2. RESULTS AND DISCUSSION

In 2009, Ashton T. Hamme II and co-workers published a paper that contains the following sequence (Scheme 4). When 2-methylene-1,3,3-trimethylindoline (**10**) reacts with a nitrile imine (generated in situ from **11a**) a spiro- Δ^2 -pyrazoline **12a** was formed that rearranged into the pyrazole **13a** (characterized by X-ray crystallography: Figure 1, refcode CORTEJ).⁹ The authors propose that the rearrangement involves the Δ^3 -pyrazoline **14a**.¹⁰

Scheme 4. Hamme's results of 2009.

Figure 1. Left side: X-ray structure of 2-(2-1,3-diphenyl-1H-pyrazol-5-yl)-N-methylaniline (**13a**).¹⁰ Right side: optimized B3LYP/6-311++G(d,p) structure of **13a**.

The X-ray structure shows a N-H $\cdots\pi$ hydrogen bond involving the aromatic electrons of the pyrazole ring. They also reported the ^1H and ^{13}C chemical shifts but without assigning them. We have used the atom numbering of Scheme 5 to prepare Table 1 where a tentative assignment was made using GIAO/B3LYP/6-311++G(d,p) calculated chemical shifts (see Computational Methods).

Scheme 5. Atom numbering of pyrazole **13a**.

In 2014, the same authors published for $\text{R} = \text{OMe}$, the study of the equilibrium **12b**/**14b**.¹¹ They reported the X-ray structure of **12b**, but the CCDC deposition number 701051 actually corresponds to **13a** although the Figure that appears in their paper is that of **12b**. They described the properties of both tautomers that depend on the solvent: in benzene (**12b**, yellow solution) and in chloroform (**14b**, pink solution). They used trifluoroacetic acid (TFAA) to transform tautomer **12b** into tautomer **14b** (Scheme 6). The latter one was stable in these conditions.

Scheme 6. Equilibrium **12b**/**14b** and protonated pyrazolinium salts.

Table 1: Calculated and experimental chemical shifts (ppm) of compound **13a**.

Atom	Calculated	Experimental	Notes
^1H NMR			
H4	6.76	6.80	under the 6.79-6.82 m, 3H
H2'	6.78	6.67	d, 2H, $J = 8$ Hz
H3'	7.04	7.07	under the 7.07 q, 3H
H4'	7.25	7.19	t, 1H, $J = 7.5$ Hz
H2''	8.00	7.91	d, 2H, $J = 7$ Hz
H3''	7.32	7.39	under the 7.33-7.46 m, 3H
H4''	7.14	7.07	under the 7.07 q, 3H
Me7	1.52	1.68	s, 3H
Me8	1.52	1.68	s, 3H
H11	6.54	6.52	d, 1H, $J = 7.5$ Hz
H12	7.31	7.39	under the 7.33-7.46 m, 3H
H13	6.52	6.40	t, 1H, $J = 7.5$ Hz
H14	6.75	6.80	under the 6.79-6.82 m, 3H
NH15	4.49	4.15	1H, broad singlet
Me16	2.56	2.71	3H
^{13}C NMR			
C3	150.2	150.9	
C4	100.9	101.0	
C5	152.9	153.0	
C1'	143.1	140.3	
C2'	129.3	128.9	
C3'	127.2	128.1	
C4'	127.8	128.3	
C1''	134.4	133.3	
C2''	124.9	126.0	
C3''	128.0	128.2	
C4''	126.9	128.1	
C6	42.8	38.0	
Me7	27.1	28.9	
Me8	27.1	28.9	
C9	131.8	129.4	
C10	148.0	147.2	
C11	109.3	110.8	
C12	128.2	128.7	
C13	115.7	116.8	
C14	126.1	125.9	
Me16	28.5	31.1	
^{15}N NMR			
N1	-163.9	----	
N2	-64.7	----	
N15	-324.3	----	

The results reported in Scheme 6 are in total contradiction to what we have summarized in the introduction. We have calculated at the B3LYP/6-311++G(d,p) level the energies of the compounds of Scheme 6 (Table 2).

Table 2: Energies (hartrees) and relative energies ($\text{kJ}\cdot\text{mol}^{-1}$) of the compounds of Scheme 5.

Compound	SCF Energy	ZPE	Total Energy	E_{rel}
12b	-1246.7844	0.47710	-1245.9917	0.0
14b	-1246.7655	0.47689	-1245.9688	49.7

It is clear that, consistently with our previous calculations (Scheme 1), a solvent effect cannot account for the existence of **14b** in chloroform.

We have calculated the absolute shieldings of the compounds of Table 1 (σ , ppm) at the GIAO/B3LYP/6-311++G(d,p) level and transformed them into chemical shifts (δ , ppm) by means of empirical equations we have established previously (see Computational Methods).

We will first discuss the case of **12b** because there is no doubt about its structure. Unfortunately, the authors reported its chemical shifts without assignment and with only the number of protons and some coupling J_{HH} values, that we have used to build up Table 3 using the numbering of Scheme 7.

Scheme 7. Numbering of **12b** used for NMR. Methyl 7 is close to C4 and the methyl 8 is close to the N1-phenyl group; H^a is close to C6 and H^b is close to N15.

The assignment was done by analogy and some errors between close signals are possible. That of Table 3 corresponds to Exp. = (1.002 ± 0.003) Calcd., $n = 37$, $R^2 = 0.999$.

In Table 4 we have reported the other compound of Table 1, the Δ^3 -pyrazoline **14b** while its numbering is in Scheme 8.

Scheme 8. Numbering of **14b** used for NMR the methyl 8 is close to the N1-phenyl group.**Table 3:** Calculated and experimental chemical shifts (ppm) of compound **12b**.

Atom	Calculated	Experimental	multiplicity, number of protons and J_{HH}
¹ H NMR			
H4 ^a	3.75	3.40	d, 1H, $J = 18.2$ Hz
H4 ^b	3.23	3.03	d, 1H, $J = 18.2$ Hz
H2'	7.07	7.03	m
H3'	6.92	6.94	m
H4'	6.61	6.73	t, 1H, $J = 7.3$ Hz
H2''	7.84	7.72	d, 2H, $J = 8.8$ Hz
H3''	6.82	6.76	m
Me7	1.35	1.10	s, 3H
Me8	1.38	1.29	s, 3H
H11	6.03	6.09	d, 1H, $J = 7.6$ Hz
H12	7.12	7.22	m
H13	6.87	6.76	m
H14	7.10	7.22	m
Me16	2.27	2.25	s, 3H
Me17	3.70	3.32	s, 3H
¹³ C NMR			
C3	142.3	141.8	
C4	41.9	39.8	
C5	102.5	100.6	
C6	52.6	55.1	
Me7	32.2	31.3	
Me8	30.8	29.1	
C9	135.2	141.8	
C10	150.9	150.8	
C11	103.3	104.8	
C12	128.6	129.8	
C13	117.8	114.6	
C14	122.1	120.8	
Me16	27.1	29.1	
C1'	145.5	147.3	
C2'	116.4	118.6	
C3'	128.2	127.5	
C4'	118.6	118.8	
C1''	126.8	126.2	
C2''	126.1	121.8	
C3''	112.7	114.6	
C4''	160.4	160.8	
Me17	52.8	55.1	
¹⁵ N NMR			
N1	-200.6	---	
N2	-54.2	---	
N15	-291.7	---	

Table 4: Calculated and experimental chemical shifts (ppm) of compound **14b**.

Atom	Calcd. 14b	Calcd. 13b	Exp.	multiplicity, no. of protons and J_{HH}
¹ H NMR				
NH2	4.55	----	----	broad singlet, 1H
H4	4.87	6.59	6.72	s, 1H
H2'	6.91	6.76	6.66	d, 1H, $J = 8$ Hz
H3'	6.95	7.04		under 6.93-7.21 m
H4'	6.63	7.25		under 6.93-7.21 m
H2''	7.70	7.92	7.82	d, 2H, $J = 8.8$ Hz
H3''	6.85	6.76		under 6.93-7.21 m
Me7	1.39	1.48	1.67	s, 3H
Me8	1.37	1.48	1.67	s, 3H
H11	5.92	6.57	6.51	d, 1H, $J = 8$ Hz
H12	7.04	7.27		under 6.93-7.21 m
H13	6.71	6.51	6.39	t, 1H, $J = 7.8$ Hz
H14	7.12	6.75	6.79	d, 1H, $J = 7.8$ Hz
NH15	----	4.46	4.14	broad singlet, 1H
Me16	2.13	2.56	2.70	d, 3H, $J = 5$ Hz
Me17	3.72	3.66	3.85	s, 3H
¹³ C NMR				
C3	147.3	150.0	150.7	
C4	98.4	100.1	100.6	
C5	109.2	152.3	152.8	
C6	55.2	42.6	38.1	
Me7	29.0	27.2	28.9	
Me8	22.1	27.2	28.9	
C9	136.1	131.6	129.5	
C10	151.4	147.7	147.3	
C11	102.7	109.4	110.7	
C12	128.4	128.3	128.2	
C13	116.6	115.9	116.7	
C14	121.7	126.3	126.1	
Me16	26.6	28.5	31.1	
C1'	148.0	143.5	140.4	
C2'	116.2	129.4	128.7	
C3'	127.9	127.0	128.1	
C4'	118.2	127.6	128.2	
C1''	123.9	126.4	127.2	
C2''	127.3	125.8	125.9	
C3''	113.3	110.8	114.3	
C4''	161.2	160.2	159.8	
Me17	52.8	53.1	55.6	
¹⁵ N NMR				
N1	-248.6	-165.6	---	
N2	-254.6	-68.1	---	
N15	-297.5	-324.6	---	

It is clear that the experimental values do not correspond to **14b**. Besides, there is an important experimental ¹H NMR datum: the N-Me group at 2.70 ppm is a doublet with $J = 5$ Hz, this is typical of a NHMe;¹² Obviously the compound is the pyrazole **13b** [**13b** and **14b** have the same mass (C₂₆H₂₇N₃O)]. It differs from pyrazole **13a** in the fact that the coupling between the methyl group Me16 and the NH (a $^3J_{HH}$) is only observed for the second one, but it is known that observing these couplings depends on the exchange rate of the amino proton.¹³ The calculated chemical shifts for pyrazole **13b** (Scheme 8) are also reported in Table 4.

Using all the available data of Tables 1 and 4 for the pyrazoles **13a** and **13b** an excellent correlation is found: Exp. = (1.000±0.003) Calcd., n = 69, R² = 0.9998. Note that the ¹⁵N chemical shifts are very different for compounds **13b** and **14b**.

Scheme 9. Left side: Atom numbering of pyrazole **13b**. Right side: optimized B3LYP/6-311++G(d,p) structure of **13b**.

3. CONCLUSIONS

The availability of standard theoretical calculations of absolute shieldings (σ , ppm) and the robustness of the empirical equations to transform them into chemical shifts (δ , ppm) has allowed to correct an structural error of the literature,¹¹ and confirm that Δ^3 -pyrazolines are stable only when both N atoms are substituted.

Computational Methods

DFT calculations were carried out using the B3LYP¹³ functional, together with the 6-311++G(d,p) basis set.¹⁴ Absolute shieldings were calculated within the GIAO approximation. All the calculations were carried out using the Gaussian 09 package.¹⁵ Empirical equations were used to transform the ¹H, ¹³C and ¹⁵N absolute shieldings into chemical shifts.¹⁶

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