A theoretical study of the structure of 6,6-dimethyl-7-nitroso-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-b]pyridine

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RESUMEN

Se han llevado a cabo cálculos DFT de la 6,6-dimetil-7-nitroso-4,5,6,7-tetrahidro-1*H*-pirazolo[3,4-*b*]piridina en lo que concierne energías, apantallamientos absolutos (GIAO) y gráficos moleculares (AIM) lo cual ha permitido determinar su estructura molecular (tautomería y conformación del grupo nitroso).

Palabras clave: Aminopirazoles; transposición; pirazolo[3,4-*b*]piridinas; RMN; cálculos DFT.

SUMMARY

DFT calculations have been carried out on 6,6-dimethyl-7-nitroso-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridine concerning energies, absolute shieldings (GIAO) and molecular graphs (AIM) to determine the molecular structure of the compound (tautomerism and conformation of the nitroso group).

Key words: Aminopyrazoles; rearrangement; pyrazolo[3,4-*b*]pyridines; NMR; DFT calculations.

RESUM

S'han realitzat càlculs DFT de la 6,6-dimetil-7-nitrós-4,5,6,7-tetrahidro-1*H*-pirazolo[3,4-*b*]piridine per obtenir energies, apantallaments absoluts (GIAO) i gràfics moleculars (AIM), que han permès determinar la seva estructura molecular (tautomeria i conformació del grup nitrós).

Paraules clau: Aminopirazoles; transposició; pirazolo[3,4-*b*]piridines; RMN; càlculs DFT.

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INTRODUCTION

Some years ago, we reported a new chemical reaction (Figure 1), where 3,5-diamino-4-isopentyl-1*H*-pyrazole (**1**) treated by sodium nitrite and hypophosphorous acid affords a 4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridine derivative (**2**)[1] instead of the expected 4-isopentyl-1*H*-pyrazole (**3**) (see also reference [2]). Pyrazole **3** was subsequently prepared and biologically evaluated by Rozas *et al.*[3,4,5].

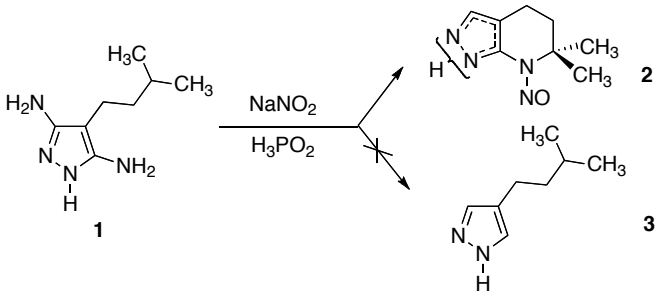


Figure 1. *The nitroso-deamination (hydro-dediazoniation)[6] of compound* ***1****.*

A number of pyrazolo[3,4-*b*]pyridines exhibit a wide range of biological activities[7], but the 4,5,6,7-tetrahydro derivatives are still rare[8]. Oxo derivatives on the six-membered ring are more common[9,10].

The mechanism of the transformation **1** → **2** is not known. Formally it corresponds to an oxidation and it probably involves a radical attack of the 5-nitrosaminopyrazole to the tertiary carbon of the isopentyl substituent with loss of H_2. The deamination of the 3-amino group could occur before or after the cyclization step (Figure 2).

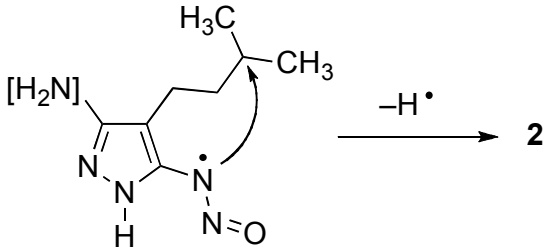


Figure 2*. A possible origin of compound* ***2****.*

Despite this reaction, leading to **2**, was described a few years ago, neither similar structures nor closely related reactions were reported. Other reactions involving nitrosation of the pyrazole ring such as 1,3-diphenyl-5-amino-pyrazole in the presence of ethyl nitrite leading to 4-hydroxyimino and azo derivatives[11], nitrosation of 5-amino-4-carboxylate nucleosides leading to a nitrosated product with several undesired side products[12], and nitrosation using $NaNO_2$ in HCl of 5-aminopyrazoles affording the 4,5-diaminopyrazoles as intermediates to 4-urea derivatives were described[13].

Although the global structure of **2** was established by ^1H, ^{13}C and ^{15}N NMR, the complete characterization of its tautomerism and isomerism, resulting if four possible structures (Figure 3), was not solved. For this reason, we decided to carry out DFT calculations at the B3LYP/6-311++G(d,p) to obtain optimized geometries and relative energies and, on the optimized geometries, to carry out GIAO calculations of the corresponding chemical shifts.

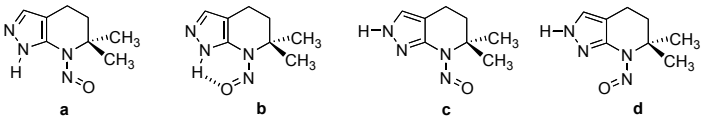


Figure 3*. The four possible isomers of* ***2****.*

COMPUTATIONAL DETAILS

The geometry of the molecules has been fully optimized with the hybrid HF/DFT B3LYP[14,15,16] computational method and the B3LYP/6-311++G(d,p) level[17,18]. Frequency calculations have been carried out at the same computational level to verify that the structures obtained correspond to energetic minima. These geometries have been used for the calculations of the absolute chemical shieldings with the GIAO method[19,20]. All the calculations have been carried out with the Gaussian-09 package[21]. The wave-functions were analyzed by means of the Atoms in Molecules (AIM)[22] theory via the AIMAll program[23].

Equations 1-3 have been used to transform absolute shieldings into chemical shifts:

$\delta^1H = 31.0 - 0.97 * \sigma^1H$ (reference TMS, 0.00 ppm)[24] *(1)*

$\delta^{13}C = 175.7 - 0.963 * \sigma^{13}C$ (reference TMS, 0.00 ppm)[25] *(2)*

$\delta^{15}N = -152.0 - 0.946 * \sigma^{15}N$ (reference ext. neat $MeNO_2$, 0.00 ppm)[25] *(3)*

RESULTS AND DISCUSSION

Geometries

For the geometries see the AIM part.

Energies

The energies of the four isomers are gathered in Table 1.

Table 1 *Absolute (hartrees), relative energies (kJ·mol^{-1}) and dipole moments (D)*

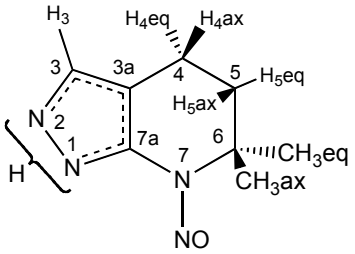
Isomer	SCF energy	ZPE	Total energy	E_{rel}	Dipole
2a	–606.38111	0.20498	–606.17613	18.2	4.04
2b	–606.38804	0.20522	–606.18282	0.0	5.11
2c	–606.37701	0.20460	–606.17241	29.0	6.13
2d	–606.37704	0.20456	–606.17248	28.9	6.09

The E_{rel} values (kJ·mol^{-1}) depend on the tautomer (1*H* or 2*H*) and the N–H···O hydrogen bond (HB). A statistical analysis lead to: intercept, 28.95; tautomer 1*H*, –10,75; NHO HB, –18.20 kJ·mol^{-1} (n = 4, R^2 = 1.000). Structure **2b which is a 1*H* tautomer and has a NHO HB is the most stable.**

NMR part

Remember that N1 and N2 corresponds to NH and to N in **2a** and **2b** and to N and NH in **2c** and **2d**; for this reason in Table 2 they will be called NH and N.

Table 2. *Calculated and experimental chemical shifts*



Atom	**2a**	**2a**, inv.	**2b**	**2b**, inv.	**2c**	**2c**, inv.	**2d**	**2d**, inv.	Exp. $CDCl_3$
NH	–201.2	–201.2	–198.7	–198.7	–107.9	–107.9	–90.6	–90.6	–174.9
N	–86.1	–86.1	–88.4	–88.4	–201.0	–201.0	–201.3	–201.3	–59.9
N7	–115.3	–115.3	–119.8	–119.8	–113.8	–113.8	–118.9	–118.9	–122.3
NO	178.0	178.0	170.4	170.4	209.4	209.4	184.6	184.6	154.2
C3	136.6	136.6	134.3	134.3	121.3	121.3	121.0	121.0	135.6
C3a	102.9	102.9	104.0	104.0	107.4	107.4	106.1	106.1	104.9
C4	18.6	18.6	18.7	18.7	18.9	18.9	19.0	19.0	16.1
C5	41.4	41.4	38.8	38.8	42.2	42.2	38.7	38.7	36.6
C6	66.0	66.0	64.7	64.7	64.8	64.8	62.8	62.8	62.3
C7a	139.2	139.2	136.1	136.1	150.4	150.4	144.7	144.7	134.8
Me6eq	26.0	22.6	27.9	26.2	25.6	22.2	28.9	26.4	26.8
Me6ax	19.1	22.6	24.5	26.2	18.8	22.2	23.9	26.4	26.8
H3	7.19	7.19	7.14	7.14	6.96	6.96	6.87	6.87	7.40
H4eq	2.63	2.56	2.62	2.68	2.50	2.60	2.69	2.73	2.68
H4ax	2.49	2.56	2.74	2.68	2.69	2.60	2.77	2.73	2.69
H5eq	1.49	1.72	2.07	1.96	1.47	1.68	1.78	1.93	2.03
H5ax	1.96	1.72	1.84	1.96	1.88	1.68	2.08	1.93	2.03
Me6eq	1.71	1.48	1.86	1.64	1.65	1.51	1.89	1.64	1.69
Me6ax	1.26	1.48	1.42	1.64	1.37	1.51	1.38	1.64	1.69
NH	9.57	9.57	11.48	11.48	8.50	8.50	8.49	8.49	9.6 (v.br)

The experimental chemical shifts were assigned in our previous work[1], where we observed that the folded ring (similar to cyclohexene or tetralin) present a rapid inversion that averaged the signal corresponding to the protons at positions 4, 6 and Me groups, as well as those of the carbons at position 6 (Me groups). Therefore, we have averaged the corresponding calculated chemical shifts in Table 2.
We have compared the experimental chemical shifts (excluding the 1H of the NH too sensitive to solvent and concentration effects) to the four calculated inv. values:

Exp. = (2.4±1.8) + (0.92±0.02) **2a**, inv., n = 19, R^2 = 0.991 *(4)*

Exp. = (2.8±1.7) + (0.93±0.02) **2b**, inv., n = 19, R^2 = 0.993 *(5)*

Exp. = (4.2±8.3) + (0.79±0.09) **2c**, inv., n = 19, R^2 = 0.824 *(6)*

Exp. = (4.4±8.7) + (0.82±1.00) **2d**, inv., n = 19, R^2 = 0.805 *(7)*

The worse point corresponds to the N atom (the receptor of N–H···N hydrogen bonds). If we remove it, eqs. (8) to (11) are found:

Exp. = (1.2±1.7) + (0.93±0.02) **2a**, inv., n = 18, R^2 = 0.994 *(8)*

Exp. = (1.4±1.3) + (0.94±0.02) **2b**, inv., n = 18, R^2 = 0.996 *(9)*

Exp. = –(7.4±5.4) + (1.00±0.06) **2c**, inv., n = 18, R^2 = 0.937 *(10)*

Exp. = –(8.5±5.4) + (1.06±0.07) **2d**, inv., n = 18, R^2 = 0.937 *(11)*

To calculate the ^{15}N NMR chemical shifts, we have used equation 3, but for compounds containing nitroso groups, in the original paper, equation 12 was proposed:

$$\delta^{15}N = -(154.0 \pm 1.9) - (0.874 \pm 0.010)\ \sigma^{15}N \quad (12)$$

Using eq. (12) we have calculated the ^{15}N chemical shifts of the four isomers (Table 3).

Table 3 *Calculated with eq. (12) and experimental ^{15}N chemical shifts*

Atom	**2a**	**2b**	**2c**	**2d**	Exp. $CDCl_3$
NH	–207.8	–197.2	–199.3	–199.5	–174.9
N	–93.1	–95.3	–113.2	–97.2	–59.9
N7	–120.1	–124.2	–118.7	–123.4	–122.3
NO	150.9	143.9	179.9	157.0	154.2

We have compared the experimental ^{15}N chemical shifts with those reported in Table 2 (compounds without nitroso groups) and Table 3 (compounds with nitroso groups) finding that for 1H-tautomers, the intercepts are better (close to 0) using the equation without nitroso groups and the slopes are better (close to 1) using the equation with nitroso groups:

Without:

Exp. = –(0.3±10.6) + (0.86±0.07) **2a**, n = 4, R^2 = 0.988 *(13)*

Exp. = (2.5±9.3) + (0.90±0.06) **2b**, n = 4, R^2 = 0.991 *(14)*

Exp. = –(8.6±15.7) + (0.79±0.10) **2c**, n = 4, R^2 = 0.972 *(15)*

Exp. = –(2.2±10.3) + (0.86±0.07) **2d**, n = 4, R^2 = 0.988 *(16)*

With:

Exp. = (12.2±11.0) + (0.94±0.07) **2a**, n = 4, R^2 = 0.988 *(17)*

Exp. = (15.7±9.7) + (0.97±0.07) **2b**, n = 4, R^2 = 0.991 *(18)*

Exp. = (3.0±16.3) + (0.86±0.10) **2c**, n = 4, R^2 = 0.972 *(19)*

Exp. = (10.4±10.7) + (0.93±0.07) **2d**, n = 4, R^2 = 0.988 *(20)*

In summary, the NMR calculations show that: i) concerning tautomerism it is absolutely clear that compound **2** is an 1*H*-tautomer; ii) concerning the conformation of the *N*-nitroso group, the differences are minor **but in all cases the compound with the HB (2b) present better correlation coefficients than 2a**; iii) although **2** contains a nitroso group, equation 3, that we have used in most papers is still the preferred one; iv) the presence of intermolecular hydrogen bonds, IMHB, that affect primarily the acceptor N atom, made this atom an outsider.

Atoms in Molecules (AIM) analysis

The molecular graphs of the four isomers considered are gathered in Figure 4. In all cases, intramolecular weak interactions are found between the oxygen atom of the nitroso group and different parts of the molecule. They are represented by the bond critical points (BCP) and their corresponding bond paths connecting the atoms involved in the interaction. In the case of **2a** and **2c**, the interactions

are with the hydrogen atoms of the gem-dimethyl group. In **2b**, a N–H···O hydrogen bond (HB) is present and in **2d** the N···O interaction obtained resembles the recently described pnicogen bonds (ZB)[26,27]. The value of the electron density in the N–H···O BCP is larger than in the rest of the contacts (0.022 *vs*. 0.016 au). In the same way the Laplacian at the BCP is 0.09 in the HB and around 0.06 au in the rest of the cases. These results confirm that the HB of **2b** is more stabilizing than the interactions found in the rest of the isomers.

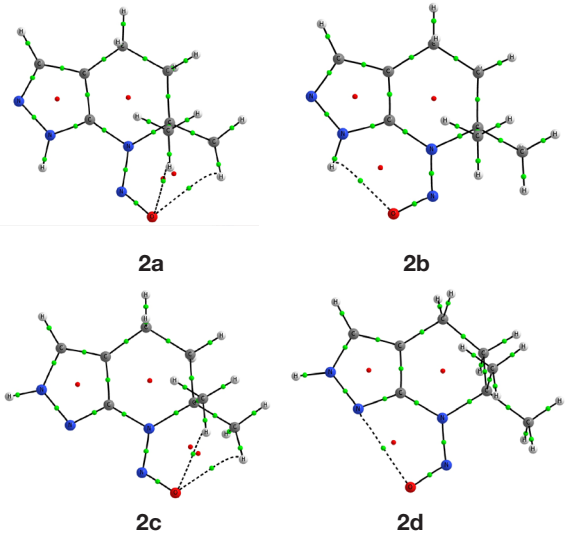


Figure 4*. The molecular graphs of the four isomers* **2a**-**2d**.

CONCLUSIONS

The most stable structure of compound **2**, i.e. **2b**, results from a combination of i) substituent effects that determine the tautomerism, and ii) hydrogen bonds that determines the conformation of the nitroso substituent. Therefore, it is possible using reported data of a compound that no longer exists, to determine its structure in solution using DFT calculated energetic and spectroscopic data.

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