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COMPARATIVE STRUCTURAL STUDIES OF 4-DIAZOPYRAZOLE DERIVATIVES BY X-RAY DIFFRACTION AND THEORETICAL INVESTIGATION

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Abstract – The X-Ray crystal and molecular structures of the 4-pyrazol derivatives 3-methyl-4-diazo-5-benzamido-1*H*-pyrazole (**4**) and 3-benzamido-5-methyl-1*H*-pyrazole (**3**) have been determined. A dimeric structure has been found for the first and polymeric for the second. A comparison of **4** with 1,3-dimethyl-4-diazo-5-benzamido-1*H*-pyrazole (**2**) shows differences in the geometrical parameters of the pyrazole ring due to electron delocalization in **2** consequent to the nitrogen negative charge in the latter. Theoretical investigation at the density functional theory (DFT) level shows difference in the molecular electronic distribution of **2** and **4**, in agreement with the structural parameters and the IR stretching frequencies of the respective carbonyl moieties.

INTRODUCTION

Previously we reported the synthesis of several 4-diazopyrazole derivatives of type (**II**) and (**IV**) prepared by reacting the related amides (**I**) and (**III**) with nitrous acid (Scheme1). Compounds (**II**) showed appreciable activity against Gram-positive bacteria such as *Staphylococcus aureus*, *Staphylococcus epidermis*, *Streptococcus faecalis* and *Listeria monocytogenes*. Moreover, some of them were active in the range 2-8 µg/mL against methicillin-resistent *Staphylococcus aureus* strains.[1] Compounds (**IV**) showed

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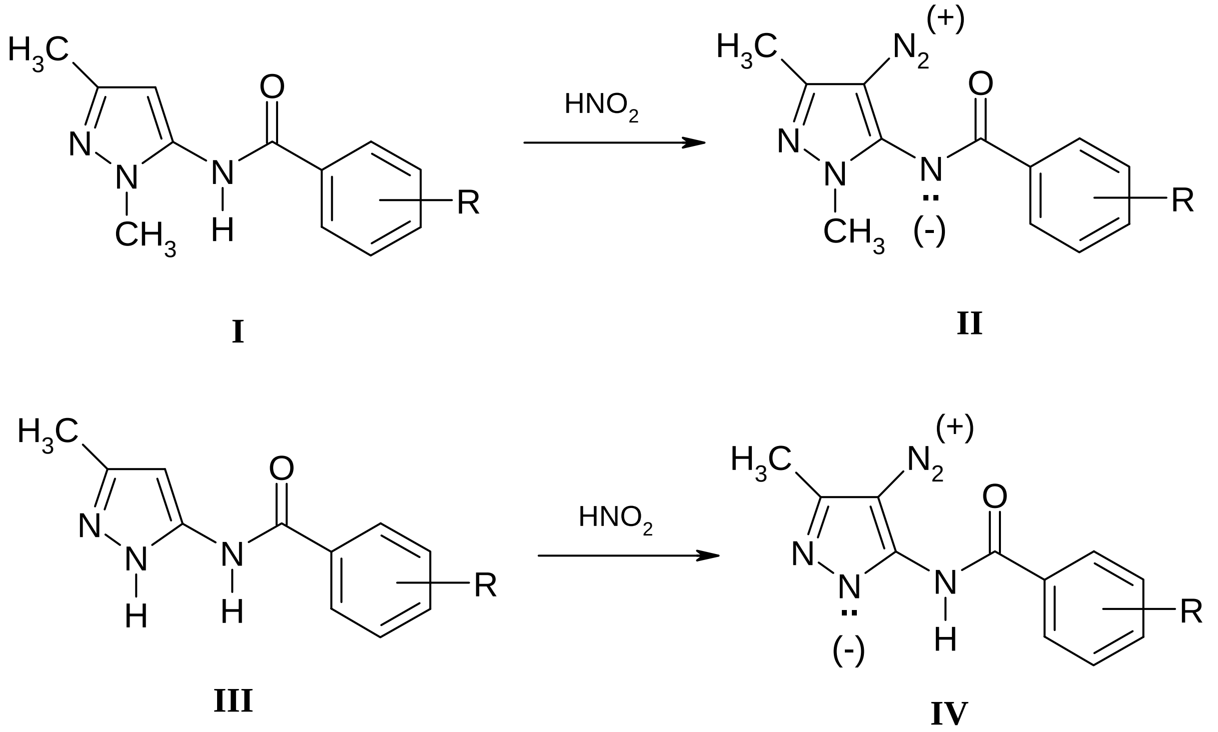
antibacterial activity against *Stapylococcus aureus*, D group *Streptococcus, Salmonella* sp. and *Shigella* sp. Moreover, they were active against a panel of human leukemia, lymphoma and solid tumor cell lines.[2]



R = H	I	II	III	IV
Comp.	1	2	3	4

Scheme 1.

The IR spectra of compounds (**II**) showed absorption bands in the 1600-1620 cm^{-1} range attributable to carbonyl group, while in compounds (**IV**) they were observed in the 1650-1680 cm^{-1} range.[1,2] For both the series, the carbonyl group absorption remained practically unchanged in the solution (CCl_4) spectra at different concentrations.

It was then thought of interest to determine the crystal and molecular structure of a type (**IV**) (R=H, **4**) representative compound in order to compare its structure with that of a type (**II**) (R=H, **2**) diazo compound, previously reported by us[1] and to explain the different IR absorption spectra of the carbonyl group. In addition the crystal structure of the starting amide of type (**III**) (R=H, **3**) was also studied with the aim to elucidate the possible changes in the structural parameters in absence of the diazo group.

RESULTS AND DISCUSSION

The crystal structure of 3-methyl-4-diazo-5-benzamido-1*H*-pyrazole (**4**) is shown in Figure 1 as ORTEP[3] view.

The overall conformation of the molecule is defined by the torsion angles O-C(6)-C(7)-C(12) of -167.25(3)° and N(1)-C(1)-N(3)–C(6) of 176.76(3)°, indicative of a significant tilting of the phenyl moiety with respect to the rest of the molecule.

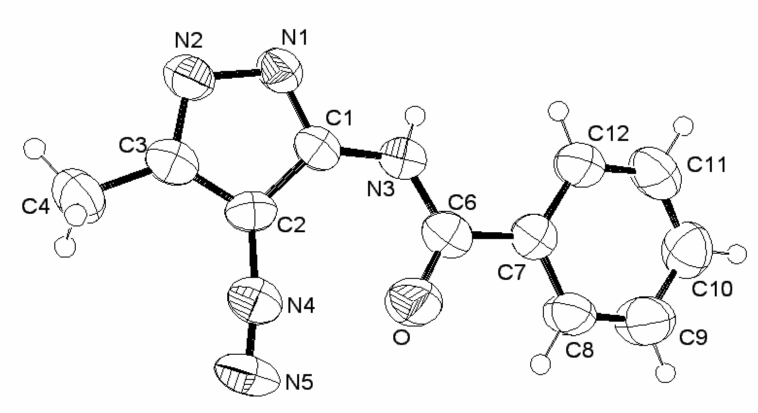


Figure 1. ORTEP[3] drawing of **4** with the atom numbering (ellipsoids are at 50% probability).

This is best evidenced by the dihedral angle of 13.54(2)° between the phenyl ring and the plane of the C(1)–N(3)–C(6)–C(7) moiety. A comparison with the dimethyl substituted analogous of type (**II**) (R=H, **2**)[1] indicates some differences in the geometrical parameters. The diazo group bond distances C(2)–N(4) 1.336(8)Å and N(4)–N(5) 1.110(7)Å are comparable to the values 1.317(6)Å and 1.116(7)Å found in the dimethylated derivative, while in the pyrazole ring the N(1)-C(1) bond distance is shorter (1.306(7) vs 1.343(5)Å) and the adjacent C(1)-N(3) is longer (1.378(8) vs 1.329(5)Å), indicating electron delocalisation due to the negative charge on the N(3) atom of the dimethylated derivative. The relative positions of N(4) and O atoms are similar in both compounds being the corresponding distances 2.459(5)Å and 2.443(8)Å for **2** and **4** respectively. The two compounds differ in the molecular packing: molecular stacking is observed in the dimethylated compound (**2**), while the absence of a methyl in **4** allows dimer formation (Figure 2), via hydrogen bond interaction involving the N(3) proton of one molecule and the N(1)′ of the pyrazole of the centrosymmetrically related molecule with a distance N(3)-H···N(1)′ of 2.415(1)Å, angle of 175.37(2)° (′ at 2-x, -y, -z).

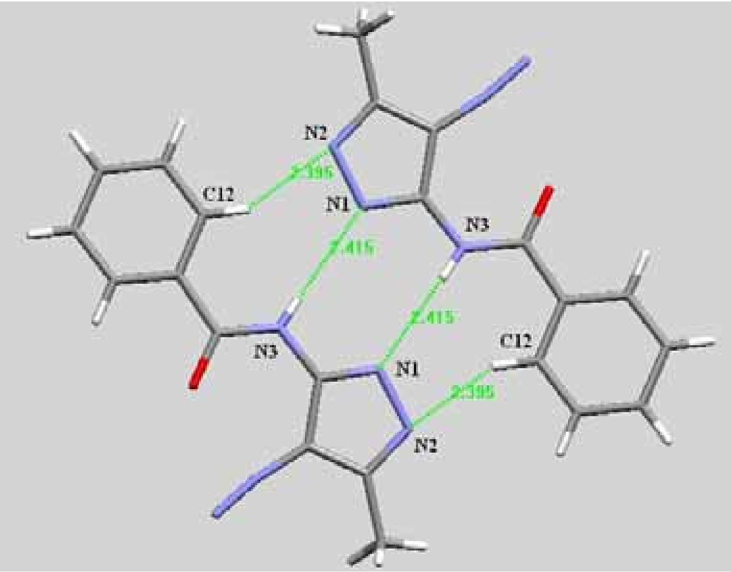


Figure 2. H-bond interactions between two symmetry related molecules of **4**.

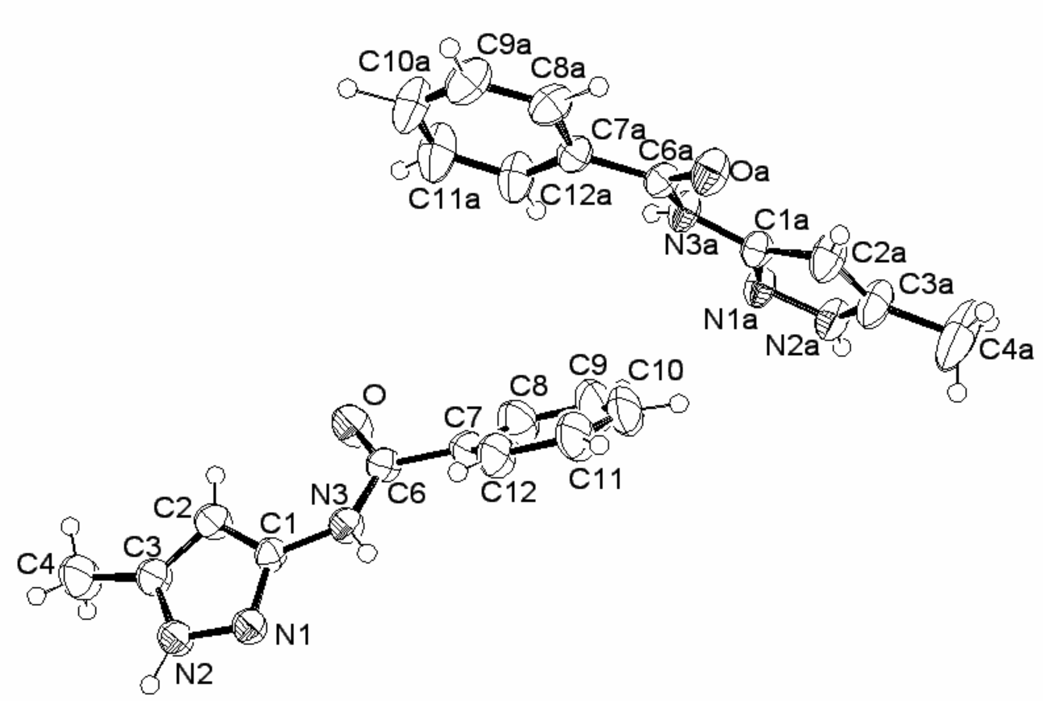


Figure 3. ORTEP[3] view of the two independent molecules of **3** with the atom numbering (ellipsoids are at 50% probability).

The molecular structure of the benzamido derivative (**3**) shown in Figure 3 is characterized by two molecules in the asymmetric unit, differing for the orientation of the phenyl group, as evidenced in Figure 4 by the superimposition of the respective planes formed by the C(6)-N(3)-C(1) moieties and by the torsion angles O-C(6)-C(7)-C(12) of 145.5(3)° and O(a)-C(6a)-C(7a)-C(12a) of –165.1(3)°. Both molecules present a trans planar conformation of the C(1)-N(3)-C(6)-C(7) and C(1a)-N(3a)-C(6a)-C(7a) fragments with torsion angles –174.3(2)° and –169.6(2)° respectively.

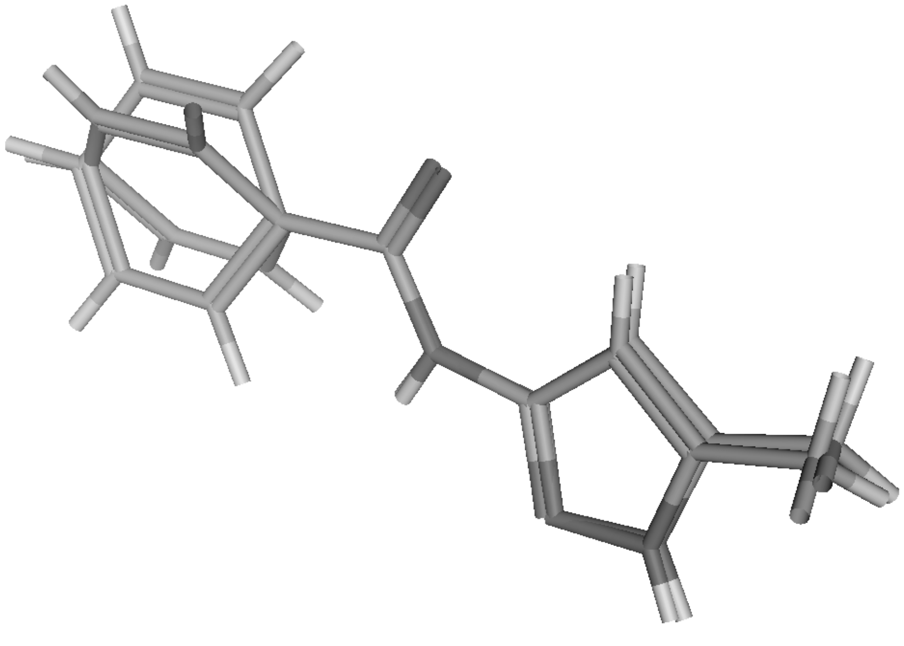


Figure 4. Superimposition of the two independent molecules of **3**.

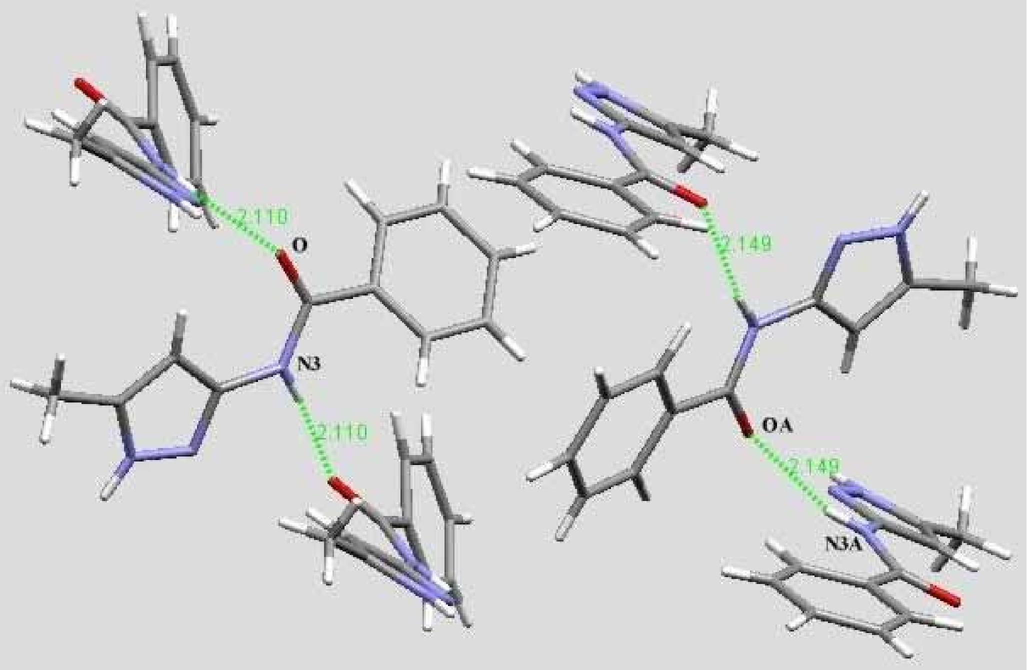


Figure 5. Chain structure of the two independent molecules of **3**.

Each of the two independent molecules forms with the adjacent of the same type a chain structure (Figure 5), due in one to an intermolecular hydrogen bond N(3)-H(3)···O′ of 2.11(3)Å, angle 175(3)° (′ at x-½, -y-½, z) and in the second *via* the hydrogen bond N(3a)-H(3a)···O(a)″ of 2.15(3)Å, angle 161(3)° (″ at ½+x, -y+½, z). Bond distances and angles are comparable in the two molecules and the different orientation of the phenyl rings does not influence a possible conjugative effect (for the more coplanar phenyl) on the respective adjacent bonds. The reported geometries allow to define the molecular structure, at least in the studied crystals, as 3-benzamido derivative and not as 5-benzamido as previously reported[2] (Scheme 1 and Figure 3). Electronic structure analysis of **2** and **4**, calculated with Gaussian-(G03)[4] was rather informative. Compound (**2**) shows a highly delocalized electronic structure (Figure 6), with the highest occupied molecular orbital (HOMO) extending from the 5-member ring to the C=O. The high delocalization of the valence electrons of **2** causes only a partial double-bond character of the C=O bond, reflected by the distance of 1.226Å, very near to crystallographic value of 1.227Å.

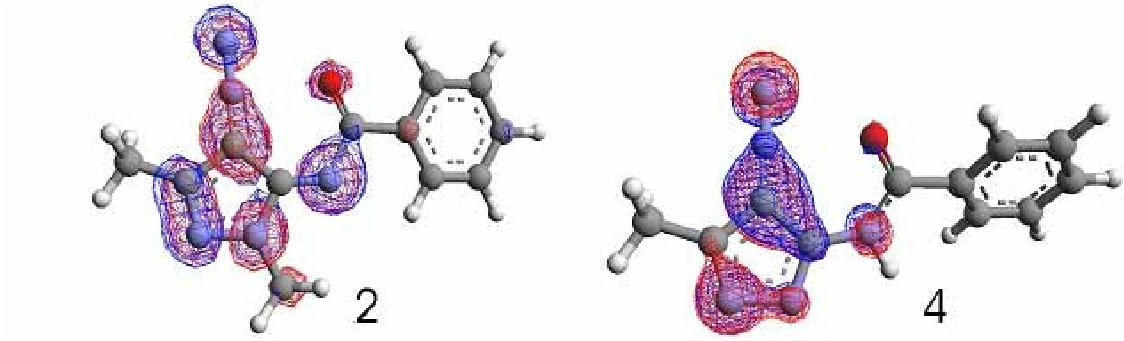


Figure 6. Iso-contour representation (contour value 0.03 au) of the HOMO for compound (**2**) and (**4**).

The delocalization in the pyrazole moiety is supported by NMR data, the ^{13}C NMR spectra of **2** show a signal at 73.46 ppm for the carbon atom bearing the diazo group, that is rather shifted at up field with respect to the starting amide (100.45 ppm).[1] The calculated $\upsilon_{C=O}$ frequencies (1626.66 cm^{-1} and 1666.44 cm^{-1} for **2** and **4**, respectively) agree with the IR spectral data.[1,2] In particular, the density functional theory (DFT) method used is able to reproduce the observed differences between the two compounds, with a $\Delta\upsilon_{C=O}$ of 39.78 cm^{-1} (experimental: $\Delta\upsilon_{C=O}$ frequency shift 45 cm^{-1}). The electronic distribution analysis of **4** shows that C=O is less involved in the electron delocalisation with the remaining structure (Figure 6), with a consequent shortening of the calculated C=O bond (1.220Å) accounting for the higher $\upsilon_{C=O}$ value for **4** with respect to **2**. The values of e.s.d.s. (due to the poor quality of the crystals) of the corresponding crystallographic distance do not allow a reliable comparison with the theoretical data that in any case are significant when compared with the experimental values of the IR frequencies. Finally, compounds (**3**) and (**4**) show the same benzamide moiety, but only the carbonyl group of **3** behaves as hydrogen bond acceptor and, as a consequence, its absorption shows a shift of 15 cm^{-1}. In conclusion, the negative charge formed early on the amide nitrogen atom of **2** is delocalized on the carbonyl group and pyrazole ring, whereas for compound (**4**) the negative charge remains delocalized in the pyrazole moiety and the carbonyl group is influenced by the mesomeric effect of the amide nitrogen. The hypothesis previously reported of an electrostatic interaction in compound (**2**)[1] between the positive charge of the diazo group and the negative of the polarized carbonyl group, in order to explain the low strength absorption of the latter group, must be rouled out as it does not work with compound (**4**).

EXPERIMENTAL

Crystallography

Crystals of **3** were obtained by slow evaporation of an ethyl acetate solution at room temperature. After four days transparent crystals in platelets shape precipitated. Crystals of **4** were obtained, after many attempts, from an ethanolic solution as transparent platelets, poorly diffracting.

They were mounted on an Enraf Nonius CAD-4 diffractometer using MoKα radiation (compound (**3**)), while for **4** a Philips PW1100 diffractometer was used. The lattice parameters were determined by least-squares refinements of 25 reflections and the space groups were determined from the observed systematic absences. The structures were solved by direct methods (SIR-92[5]) and the refinements were carried out by full-matrix anisotropic least-squares for non-hydrogen atoms. The hydrogen atoms were included at their calculated positions, riding on their parent atoms, and refined isotropically in **4** while in **3**, except for those of the methyls introduced at calculated position, they were detected in the fourier map and refined isotropically. Refinements were carried out by using SHELX-97 package[6] and by WINGX.[7] Crystallographic and refinement data for the two structures are presented in Table 1; selected bond lengths and angles are reported in Table 2. (the geometrical parameters of compound (**2**) are reported for comparison)

The supplementary crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC deposition numbers 275436 and 275693). Copies can be obtained, free of charge, from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223) 336033; e-mail: deposit@ccdc.cam.ac.uk).

Table 1. Crystal data and structure refinement for **3** and **4**.

	3	**4**
Empirical formula	$C_{11}H_{11}N_3O$	$C_{11}H_8N_4O$
Formula weight	201.23	212.21
Temperature(K)	293(2)	293(2)
Wavelength(Å)	0.7107	0.7107
Space group	$P2_1/a$	$P2_1/c$
Unit cell (Å,°)	a=9.290(6)	a=5.449(2)
	b=11.074(4)	b=8.663(2)
	c=20.876(5)	c=22.778(4)
	β=100.91(1)	β=94.46(3)
Volume(Å ^{3})	2108.9(1)	1072.0(1)
Z, Calc.density (Mg/m ^{3})	8, 1.268	4, 1.3149
Absorption coeff. (mm $^{-1}$)	0.085	0.090
F(000)	848	440
Crystal size (mm)	0.5x0.5x1	0.2x0.2x0.7
θ range (°)	2.1 -25	3-25
Limiting indices	-11≥h≥10	-6≥h≥6
	-1≥k≥13	0≥k≥10
	-1≥l≥24	0≥l≥27
Refl. collected/unique	4465/3692	1528/1312
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/param.	3692/0/337	1312/0/160
Goodness-of-fit on F^2	0.98	1.33
Final R indices	R1=0.0434	R1=0.10
[I>2σ(I)]	wR2=0.1202	wR2=0.23

Table 2. Selected bond lengths [Å] and angles [°] for **3**, **4** and **2**[1].

Compound	**3**	**4**	**2**
O-C(6)	1.235(3) [1.236(3)]*	1.231(7)	1.227(5)
N(2)-C(3)	1.341(3) [1.334(3)]*	1.313(8)	1.297(6)
N(1)-N(2)	1.360(3) [1.354(3)]*	1.416(7)	1.382(5)
N(1)-C(1)	1.323(3) [1.324(3)]*	1.306(7)	1.343(5)
N(5)-N(4)		1.110(7)	1.116(7)
N(4)-C(2)		1.336(8)	1.317(6)
N(3)-C(6)	1.339(3) [1.336(3)]*	1.351(8)	1.354(5)
N(3)-C(1)	1.398(3) [1.401(3)]*	1.378(8)	1.329(5)
C(1)-C(2)	1.392(3) [1.385(3)]*	1.448(8)	1.438(6)
C(2)-C(3)	1.373(4) [1.366(4)]*	1.392(9)	1.429(6)
C(3)-C(4)	1.486(3) [1.492(4)]*	1.495(9)	1.480(6)
C(6)-C(7)	1.490(3) [1.489(3)]*	1.483(9)	1.498(5)
C(3)-N(2)-N(1)	112.6(2) [112.4(2)]*	108.8(5)	106.7(4)
C(1)-N(1)-N(2)	103.6(2) [103.9(2)]*	109.2(5)	114.7(4)
N(5)-N(4)-C(2)		170.7(7)	171.0(6)
C(6)-N(3)-C(1)	125.8(2) [125.7(2)]*	124.2(6)	117.9(3)
N(1)-C(1)-N(3)	117.1(2) [116.5(2)]*	120.6(6)	120.5(4)
N(1)-C(1)-C(2)	112.5(2) [112.1(2)]*	107.2(5)	101.8(4)
N(3)-C(1)-C(2)	130.4(2) [131.3(2)]*	132.2(6)	137.7(4)
N(4)-C(2)-C(3)		122.9(6)	120.8(4)
N(4)-C(2)-C(1)		131.1(6)	131.4(4)
C(3)-C(2)-C(1)	104.6(2) [104.8(2)]*	106.0(5)	107.8(4)
N(2)-C(3)-C(2)	106.7(2) [106.9(2)]*	108.8(6)	109.0(4)
N(2)-C(3)-C(4)	122.8(2) [122.3(3)]*	123.1(6)	124.2(4)
C(2)-C(3)-C(4)	130.5(2) [130.8(3)]*	128.1(6)	126.8(4)
O-C(6)-N(3)	122.3(2) [122.1(2)]*	120.3(7)	125.4(4)
O-C(6)-C(7)	120.8(2) [120.6(2)]*	120.6(6)	120.1(4)
N(3)-C(6)-C(7)	116.9(2) [117.3(2)]*	119.1(6)	114.5(3)

*The asymmetric unit is formed by two independent molecules

Theoretical calculations

The geometry optimization run was performed on both **2** and **4**, with the DFT method, using the Gaussian-03 (G03) program package. Gaussian-03 Dunning's polarized valence double-ξ basis sets[8] were used for N and O. The hybrid Becke's three parameters functional with the Lee, Yang and Parr correlation functional (B3LYP)[9] have been used in both the optimization and frequency calculations steps (G03/B3LYP). The vibrational analysis results, together with the eigenvalues of the Hessian matrix, were also used as a test for the character of the stationary point found on the molecular potential energy hyper-surface, stationary point that corresponds to the real minimum for the two compounds. The predicted frequencies were then scaled by a multiplicative, method dependent constant, to eliminate known systematic errors, like that arising from the basis set truncation.

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