JOC Article

Structure of a 4-Nitroso-5-aminopyrazole and Its Salts: Tautomerism, Protonation, and *E*/*Z* Isomerism

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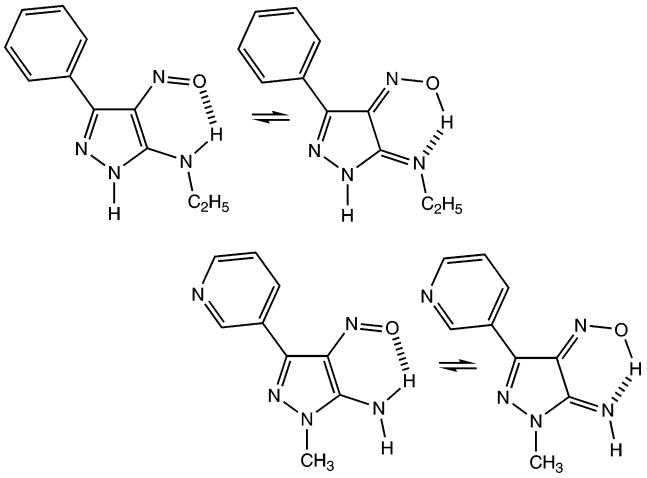
Received June 16, 2003

The structures of 1-benzyl-4-nitroso-5-aminopyrazole (**1**) and its hydrochloride (**1H**$^+$) have been determined in the solid state and in solution in DMSO, methanol, and ethanol. The free base exists in solution as a mixture of amino/nitroso tautomers **2a** and **2b** rather than in the imino/oxime tautomers **3**. The conjugated cation **1H**$^+$ results from the protonation of the nitroso group. X-ray crystallography showed that both amino hydrogen atoms of **2a** form NH···O═N hydrogen bonds: one is intramolecular, the other links adjacent molecules in an infinite chain.

Introduction

Recently, one of us has reported that the hydrochloride of 1-benzyl-4-nitroso-5-aminopyrazole (**1H**$^+$, compound **5** in ref 1, conjugated base **1**) presents all the NMR signals duplicated (for instance, in the ^{13}C NMR spectrum, 16 resonances instead of the eight expected for **5**).[1] Conjugated nitroso-amines belong to the same family as the enols of β-diketones and other conjugated systems with intramolecular hydrogen bonds (IMHB), called by Gilli "Resonance Assisted Hydrogen Bonds", RAHB.[2] The CC double bond can be part of an aromatic or heteroaromatic ring[3] and, except for the intramolecular hydrogen bond, the kind of tautomerism is the same for para-substituted benzene derivatives. For instance, Reichardt reports that 4-nitrosophenol exists in solution mainly in the 1,4-benzoquinone monoxime form.[4a] For the following discussion, we will also note that Reichardt's pyridinium-*N*-phenoxide betaine shows thermo-solvatochromism: in ethanol at −75 °C the solution is red (513 nm), and at +75 °C the solution is blue-violet (568 nm).[4b]

In the case of pyrazoles bearing at position 4 and 5 respectively an amino and a nitroso group, there were two previous reports: Junjappa et al.[5] discussed the tautomerism of several 1*H*-3-phenyl-4-nitroso-5-alkylaminopyrazoles



In the solid state, this compound appears as orange crystals; its UV spectrum in methanol displayed a band at λ_{max} 573 nm (ϵ 96) characteristic of the nitroso group, which led the authors to rule out the oximino tautomer.[5] At about the same time, Fray et al.[6] reported a similar observation for a series of 1-methyl-3-heteroaryl-4-nitroso-5-aminopyrazoles. They commented that some of these compounds were isolated as bright red solids while others were dark olive green, both giving green solutions

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(4) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; VCH: Weinheim, Germany, 2003; (a) p 118, (b) p 428.
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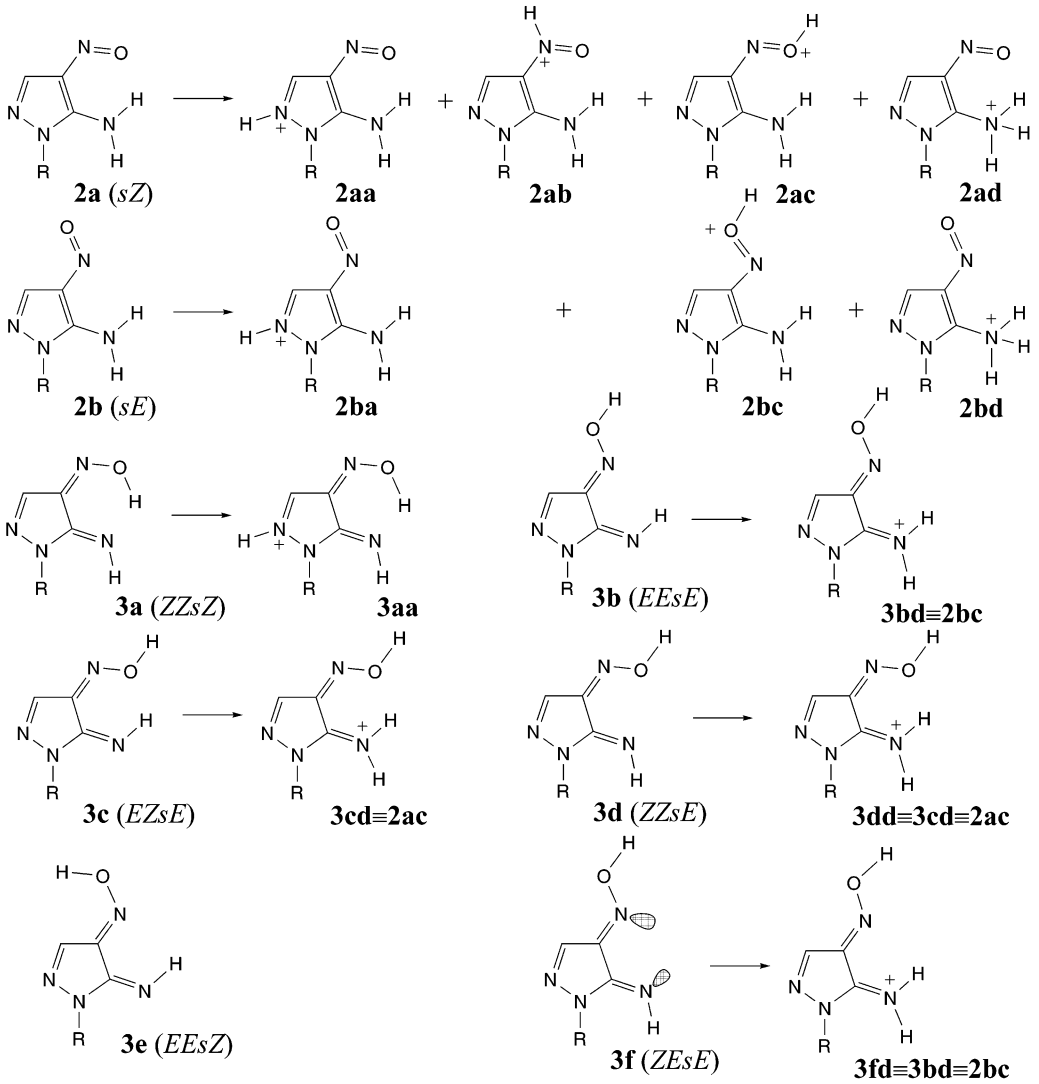
10.1021/jo034833u CCC: $25.00
Published on Web 10/24/2003

SCHEME 1



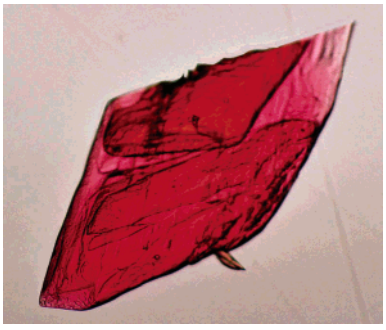


FIGURE 1. Crystals of compound **1**.

when dissolved in ethyl acetate or DMSO. They attributed this behavior to the rapid conversion of the oximino (red) to the nitroso (green) tautomer in solution.

Results and Discussion

Hydrochloride **1H**$^+$ is yellow[1] but when neutralized by column chromatography over silica affords the free-base as orange-red solid **1** (see Figure 1) whose solutions are, for instance, red in ethanol and blue-violet in DMSO (those of **1H**$^+$ are yellow in all solvents).

We have used the following convention for naming the neutral species: **1** represents the compound without any tautomeric and isomeric definition; **2** and **3** are the nitroso (two rotamers **a** and **b**) and the oxime tautomers (6 conformations **a** to **f**). These compounds have four lone pairs available for protonation affording four cations designed by a second letter: **a** (protonation on the ring N2 nitrogen atom), **b** (protonation on the nitrogen atom of the nitroso or oxime substituent), **c** (protonation on the oxygen atom of the nitroso or oxime substituent), and **d** (protonation on the amino or imino groups). In Scheme 1 are reported only the molecules we have calculated, a small subset of all possible structures corresponding to the most stable species. Note that **3f** is the only structure in Scheme 1 that has not been calculated because the repulsion of the lone pairs would make this structure very unstable.

Concerning the *E*/*Z*, *sE*/*sZ* nomenclature, in the case of the nitrosopyrazole isomers, the *Z*/*E* system used in Scheme 1 refers to the orientation of the N=O bond with respect to the amine NH. In the case of the oximepyrazole isomers, the first isomerism refers to the C=N−H double bond, the second isomerism refers to the C=N−OH

FIGURE 2. Methanol (red) and ethyl acetate (blue-green) solutions of compound **1**.

double bond, and the third one (*sE*/*sZ*) concerns the =N−O−H single bond.

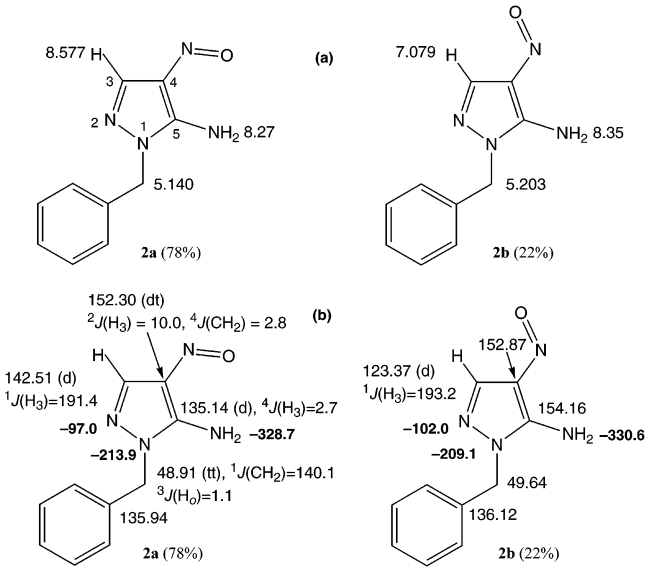
The experimental study was carried out on the 1-benzyl derivatives of **1** and **1H**$^+$, while the theoretical calculations were carried out on the 1-methyl derivatives, considering that the 1-substituent should have negligible effects on the relative energies and on the NMR shieldings of the pyrazole moiety while considerably shortening the computing time. Note that some cations are formed from different neutral molecules.

Neutral Molecule 1. Compound **1** exists in methanol, ethanol, and DMSO-d_6 as a mixture of rotamers **2a** and **2b** (R = Bn) without any observable amount of oximes **3**. A solution of **1** in ethanol is red while in ethyl acetate it is blue-green (see Figure 2).

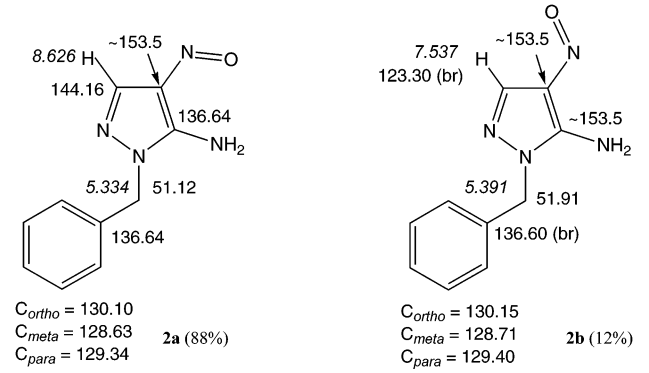
(1) Electronic Spectra. Aromatic nitroso compounds are characterized by a weak n → p* transition that appears in the visible region between 680 and 760 nm (ϵ = 40−70) and is sensitive to solvent polarity.[7] The spectrum of **1** in ethanol shows peaks at λ_{max} 288.5 (ϵ 9800), 350 (ϵ 5900), and 558 nm (ϵ 60), which is consistent with a nitroso or a mixture of nitroso derivatives (**2a** and **2b**).[5] By analogy with Reichardt's betaine thermosolvatochromism,[4b] we have recorded the spectrum in ethanol between +20 and −20 °C and observed that it remains unchanged, in particular the 558-nm band does not significantly change its position or its intensity. In ethyl acetate (blue solution, see Figure 2) the compound absorbs at λ_{max} 282 (ϵ 7450), 344 (ϵ 5640), and 603 nm (ϵ 90).

(2) NMR Spectra. The ^{1}H NMR spectrum in DMSO-d_6 shows a mixture of 78% of **2a** and 22% of **2b** as determined by integration of the CH_2 signals (Scheme 2a, values in ppm). That ratio did not change significantly between 23 and 50 °C, and there was no broadening of the signals. The aromatic protons of both rotamers appear between 7.15 and 7.37 ppm. A ROESY experiment shows negative off-diagonal proximity peaks between the CH_2 and the NH_2 as well as between the CH_2 and the ortho-protons for each rotamer. A positive cross-peak is observed between both H(3) signals, indicating that there

SCHEME 2



SCHEME 3



exists a dynamic, albeit slow, interconversion process between both structures.

The same ratio 78/22 can be measured on the CH_2, the H(3), and, most significantly, on the NH_2 signals. The integration of both $-NH_2$ signals equaled 2 hydrogens, ruling out oxime tautomers **2**−**8**, but that evidence did not indicate whether **2a** or **2b** was the major rotamer. The ^{13}C NMR spectrum of the same sample has been completely assigned to each rotamer thanks to a series of 2D-experiments (Scheme 2b, the CH aromatic carbons are not reported).

The coupling constants (in Hz) are similar to those of other pyrazoles,[8] but these do not discriminate between **2a** and **2b**. Likewise, a gs-HMBC (^{1}H, ^{15}N) NMR experiment identified two rotamers ($^1J_{NH}$ = 86.0 Hz for both), but could not assign their structures. The nitroso resonance expected at about + 350 ppm was not present. The signal of the nitroso group, expected at about +350 ppm, was not observed in the spectrum.

A ^{1}H and ^{13}C NMR study of **1** was carried out in methanol-d_4. At 21 °C the following results were obtained (Scheme 3).

Some signals of the less abundant isomer, **2b**, are broadened indicating that a dynamic equilibrium be-

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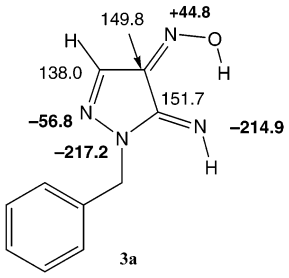
SCHEME 4



tween **2a** and **2b** exists. In CD_3OD we have recorded the ^1H NMR spectra at +21, +5, −20, −40, and −60 °C. The chemical shifts change with the temperature in a regular way [the best fits correspond to $\delta = a + bT(K) + cT(K)^2$, with $r^2 \approx 1.00$], which allows the identification of some signals that are close to the aromatic protons or the water signal. At $T = 0$ K, the values should be 8.69 and 5.39 ppm [H(3) and CH_2 of **2a**] and 9.20 and 5.39 ppm [H(3) and CH_2 of **2b**]. A plot of the logarithm of the equilibrium constant (defined as [**2a**]/[**2b**]) vs $1/K$ leads to $\Delta G = -4.5$ kJ mol^{-1}, $\Delta H = -3.1$ kJ mol^{-1}, and $\Delta S = 5.7$ J mol^{-1} K^{-1}. These results are consistent with the fact that the electronic spectrum (see above) does not change between +20 and −20 °C, assuming that the two nitroso rotamers have the same spectral properties.

(3) Theoretical Calculations. (a) Absolute Shieldings. To assign the signals of **2a** and **2b** we have carried out GIAO-DFT absolute shielding calculations on these compounds as well as on the oximes **3a**, **3b**, **3c**, **3d**, and **3e** (Scheme 1). The comparison between calculated and experimental values allows us to exclude the oximes, to ascertain the assignments, and to identify **2a** and **2b**. The correlation of experimental δ values against calculated σ values (Equations 1, including TMS, and 2) allows the prediction of the δ values for the most stable oxime (**3a**, Scheme 4) which are very different from those of the amino-nitroso derivatives **1**.

$$^{13}\text{C NMR: } \delta\ (\text{ppm}) = (176.9 \pm 2.6) - (0.94 \pm 0.03)\sigma\ (\text{ppm}),\ n = 7,\ r^2 = 0.994 \quad (1)$$

$$^{15}\text{N NMR: } \delta\ (\text{ppm}) = -(157 \pm 1) - (0.86 \pm 0.01)\sigma\ (\text{ppm}),\ n = 6,\ r^2 = 0.999 \quad (2)$$

(b) Energies. The energies of the different tautomers and isomers of Scheme 1 have been calculated (B3LYP/6-311++G**). The structures can be ordered based on their relative energies (in parentheses in kJ mol^{-1}) with regard to the most stable (**2a**): **2a** (0.0) > **2b** (11.2) > **3a** (22.6) > **3b** (28.5) > **3c** (28.6) > **3d** (49.6) > **3e** (56.8).

(4) Restricted Rotation about the C(4)−NO Bond. A question that could arise is if the barrier about this bond is large enough to justify the observation of separate signals in ^1H NMR, signals that remain narrow even at 70 °C. Gowenlock, Orrell, et al. reported that 4-nitrosopyrazoles show average signals for the substituents at positions 3 and 5 at room temperature (30 °C) in ^1H NMR but that on cooling they separate allowing the determination of the barrier ($\Delta G^{\ddagger} = 50.8$ kJ mol^{-1} for 3,5-dimethyl-4-nitrosopyrazole).[9]

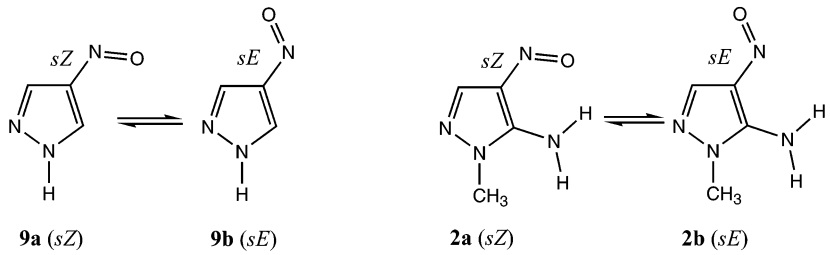
We have calculated the barriers for 4-nitrosopyrazole **9** (Scheme 5): from *sE* to the transition state (TS) 52.6 kJ mol^{-1} and from *sZ* to TS 50.3 kJ mol^{-1}. These values together with the fact that the *sE* isomer is more stable than the *sZ* one (2.3 kJ mol^{-1}) agree with the reported experimental result.[9] The presence of an amino group at position 5 (compound **2**, Scheme 5) considerably increased the calculated barriers (from *sZ* to TS 91.4 kJ mol^{-1} and from *sE* to TS 80.2 kJ mol^{-1}) and inverted the stability between both rotamers (11.2 kJ mol^{-1} in favor of the *sZ* **2a**). The increase in the barrier and the stability inversion, which justifies the observation of **2a** and **2b** at room temperature, is a consequence of both the resonance effect of the amino group and the IMHB that stabilizes the **2a** structure. As expected, the nitroso group deshields H-3 of **2b** to a greater extent than that of **2a**.

(5) Solid State: CPMAS NMR and Crystallography. The ^{13}C and ^{15}N CPMAS NMR spectra of the crystalline orange-red solid correspond to structure **2a** (Scheme 6). Thus, the crystals, although red, are of pure **2a** and when dissolved became a mixture of **2a** and **2b**. Figure 3 shows the structure of **2a** determined by X-ray on the same sample.

Except for the *N*-substituent, the geometries of **2a** (R = $CH_2C_6H_5$, experimental) and **2a** (R = CH_3, calculated) are very similar in distances, bond angles, and dihedral angles (Figure 4). The N−H distances are shorter in crystallography (about 0.95 Å) than in the calculated geometry (about 1.0 Å). The largest difference concerns the N=O bond distance (exptl 1.293 Å, calcd 1.248 Å) and may be due to the fact that in the crystal the oxygen atom is also involved in an intermolecular hydrogen bond.

Cation 1H$^+$: (1) Electronic Spectra. The spectrum of salt **1H**$^+$ in DMSO or methanol (or that of **1** containing a drop of HCl) lacks the band at 558 nm. There is no new band near 500 nm and the solution is pale yellow. Therefore, the nitroso band disappears by protonation and only two bands remain at 286 (ϵ 6450) and 350 nm (ϵ 3550).

SCHEME 5



9a (*sZ*) **9b** (*sE*) **2a** (*sZ*) **2b** (*sE*)

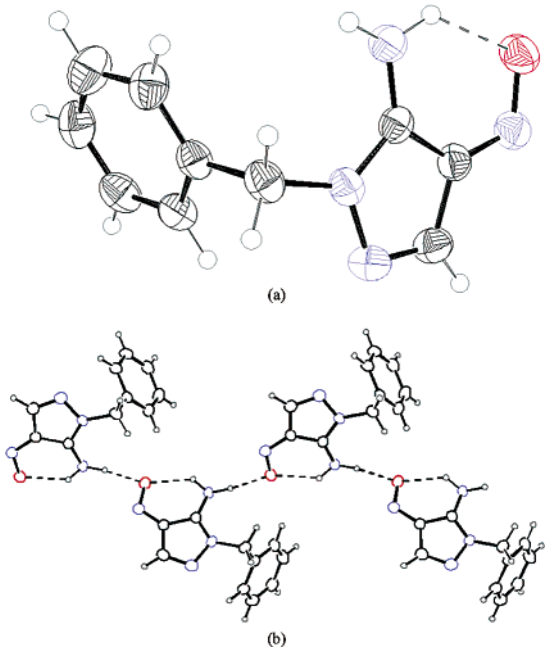


FIGURE 3. ORTEP diagram[26] of (a) the independent molecule and (b) one chain for compound **2a**.

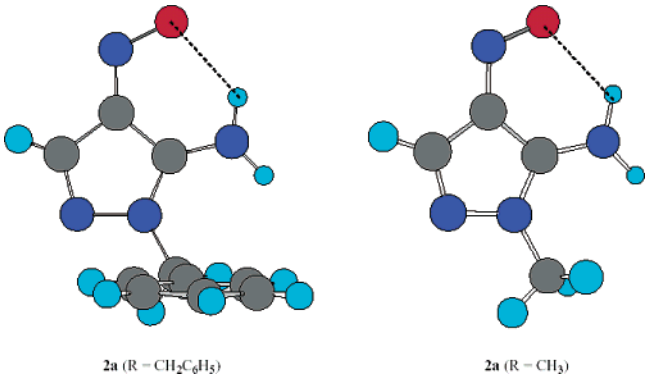
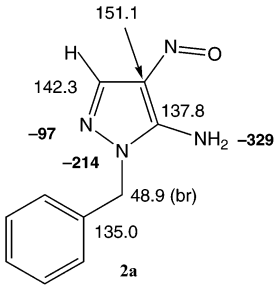


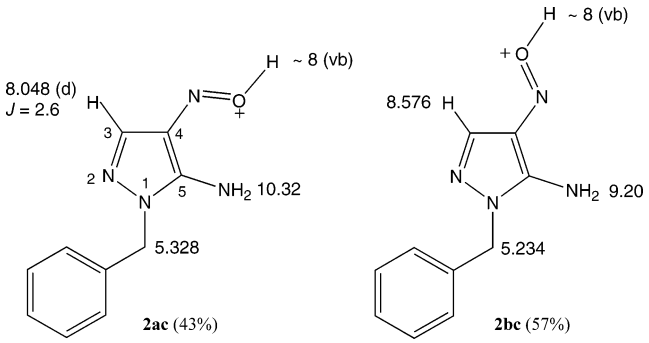
FIGURE 4. Comparison of the geometries of **2a** (R = $CH_2C_6H_5$, experimental) and **2a** (R = CH_3, calculated).

SCHEME 6

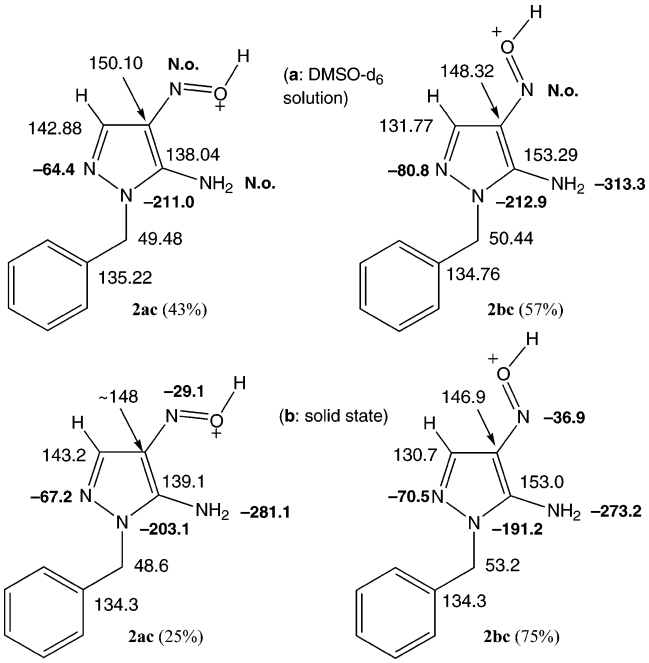


(2) NMR Spectra. The ^{1}H NMR spectrum of **1H**$^+$ in DMSO-d_6 at 22 °C is reported graphically in Scheme 7 (in CF_3CO_2H the values are similar). The first observation is that the proportions of the two isomers are much more alike. However, the proportions depend on the quality of the solvent; for instance, the presence of water increases the amount of **2bc**. We will prove that the major isomer is **2bc** and the minor isomer **2ac**. The first indication in this regard is that H(3) in **2ac** is coupled with the OH (J = 2.6 Hz) while the signal of **2bc** appears as a singlet, an observation consistent with the fact that in homoallylic coupling constants $^5J(HH)_{trans} \approx 2.5$ Hz while $^5J(HH)_{cis} \approx 1$ Hz.[10]

SCHEME 7



SCHEME 8



On heating, up to 70 °C, the coupling of **2ac** disappears, the signals at 10.32, 9.20, and 8 ppm coalesce (8.5 ppm, very broad), and the population of **2bc** increases up to 65%. It is again the comparison of experimental (Scheme 8a) and calculated ^{13}C NMR shieldings (GIAO-DFT) that establishes the identity of the two isomers. Equation 3 includes neutral molecules and cations:

$$^{13}\text{C NMR: } \delta\ (\text{ppm}) = (176.4 \pm 1.5) - (0.94 \pm 0.02)\sigma\ (\text{ppm}),\ n = 13,\ r^2 = 0.993 \quad (3)$$

Since for this salt no convenient single crystals could be obtained, the approach to the solid state is based exclusively on ^{13}C and ^{15}N CPMAS NMR (Scheme 8b). For ^{15}N NMR the results are more complete but the four available data common to DMSO and CPMAS are related

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(eq 4). Considering the effects produced on the chemical shifts by the interactions present in the solid state, eq 5 relates CPMAS values and calculated σ values.

$$^{15}\text{N NMR: } \delta\,(\text{DMSO}) = (1.07 \pm 0.03)\delta\,(\text{CPMAS}),\ n = 4,\ r^2 = 0.998 \quad (4)$$

$$^{15}\text{N NMR } \delta\,(\text{ppm}) = -(170 \pm 5) - (0.62 \pm 0.01)\sigma\,(\text{ppm}),\ n = 6,\ r^2 = 0.986 \quad (5)$$

Taking into account the proximity of the anion in the solid state, the chemical shifts of Scheme 8a,b are very similar, proving that the solid is also a mixture of **2ac** and **2bc**. However, the ratio is not the same, 43/57 in DMSO and 25/75 in the solid. Therefore, the solution values correspond to an equilibrium.

(3) Theoretical Calculations: Energies. The energies of the different cations of Scheme 1 have been calculated (B3LYP/6-311++G**). With regard to the most stable structure (**2bc**), the order of decreasing stability (in parentheses, kJ mol^{-1}) is the following: **2bc** (0.0) > **2ac** (1.8) > **2ab** (18.2) > **2aa** (42.8) > **2ba** (53.7) > **3aa** (103.9) > **2ad** (140.5) > **2bd** (153.5). Only the two most stable isomers, **2bc** (57%)/**2ac** (43%), and in amounts consistent with the calculations, are observed.

Pyrazoles usually protonate on N(2) to form cations such as **2aa**, **2ba**, and **3aa**.[11−13] Even 3- and 5-amino-substituted pyrazoles protonate on N(2) and not on the amino group (to form cations such as **2ad** and **2bd**), while 4-aminopyrazoles protonate on the amino group.[14,15] There is a theoretical paper [MP2(fc)/6-31G**//HF/6-31G*+ZPE(HF/6-31G*) calculations] on the protonation of nitroso-benzene.[16] According to the authors, nitrosobenzene protonates on the nitrogen atom; however, the proton affinities of nitrogen and oxygen atoms in this compound are relatively close implying that much more accurate calculations are necessary for an ultimate assignment. In our case, the cation **2ab** (*N*-protonation) lies 18.2 kJ mol^{-1} above the **2bc** (*O*-protonation). We assign this difference to the conjugative effect of the amino group at position 5. Compounds **2** are vinylogs of nitrosamines and *N*-nitroso compounds, and nitrosamines are known to protonate on the oxygen.[17]

Conclusions

In conclusion, the free base **1** in DMSO-d_6 solution is a mixture of **2a** and **2b** while the hydrochloride salt **1H**$^+$ is a mixture of **2ac** and **2bc**. Moreover, protonation inverts the relative proportions: **2a** (78%) → **2ac** (43%) and **2b** (22%) → **2bc** (57%). The changes in color of a solvatochromic compound in solution are due to modifications of the electronic distribution (polarity, polarizability, hydrogen bonds, ...) and, in general, do not imply proton transfer (tautomerism).[4] Compound **I** is a dye that has solvatochromic properties. In the literature, these properties, for **1** and related compounds, have been assigned to a change in tautomerism: oxime red and nitroso blue-green.[5,6] Our results demonstrate that the solvatochromism of **1** is due exclusively to the nitroso tautomers **2**.

Experimental Section

General. The following instruments have been used: a UV/vis spectrometer provided with a cryostatic cooling device to modify the temperature of the cell and a mass spectrometer, using the electrospray positive mode.

1-Benzyl-4-nitroso-5-aminopyrazole (2). The hydrochloride was chromatographed at medium pressure over a silica gel with ethyl acetate−methanol as eluent. The free base was recovered: mp 158−160 °C; $C_{10}H_{10}N_4O$, calcd C, 59.40, H, 4.98, N, 27.71, found C, 59.32, H, 5.07, N, 27.63; MS 202, obsd 203.2 (M + H), 225.1 (M + H + Na), 427.2 (2Me + Na).

1-Benzyl-4-nitroso-5-aminopyrazole hydrochloride (2H$^+$).[1] **2H**$^+$ decomposes on heating. MS 202 (M).

NMR Spectroscopy. ^{1}H, ^{13}C, and ^{15}N NMR spectra in solution were obtained at 499.88, 125.71, and 50.68 MHz, respectively, on a spectrometer with a 5-mm inverse-detection H−X probe equipped with a gradient coil. Spectra were recorded under standard conditions in DMSO-d_6 with TMS as internal reference for the ^{1}H and ^{13}C spectra and CH_3NO_2 as external reference for ^{15}N spectra. The 2D-ROESY spectrum with a 200-ms spin-locking pulse was obtained with use of a 1024 × 256 point data matrix, 16 scans per increment, and processed with 2048 × 1024 points. The [^{1}H,^{13}C] gs-HSQC and the gs-HMBC spectra were obtained with use of a 1024 × 256 point data matrix, 8 scans per increment, and processed with 2048 × 1024 points. Spectral widths of 8 000 and 21 367 Hz were used in the *F*2 (^{1}H) and *F*1 (^{13}C) domains, respectively. gs-HMBC was optimized for a 8 Hz scalar coupling. The [^{1}H,^{15}N] gs-HMBC spectrum was obtained with use of a 2048 × 512 point data matrix, 96 scans per increment, and processed with 2048 × 1024 points. Spectral widths of 8 000 and 50 000 Hz were used in the *F*2 (^{1}H) and *F*1 (^{15}N) domains, respectively. gs-HMBC was optimized for a 8 Hz scalar coupling.

Solid-state ^{13}C (100.73 MHz) and ^{15}N (40.60 MHz) CPMAS NMR spectra have been obtained on a 400 spectrometer at 300 K with use of a 4 mm DVT probehead at rotational frequencies of 5−6 kHz. Samples were carefully packed in ZrO_2 rotors and the standard CPMAS pulse sequence and NQS technique were employed.[18] ^{13}C spectra were originally referenced to a glycine sample and then the chemical shifts were recalculated to the Me4Si (for the carbonyl atom d(glycine) = 176.1 ppm) and ^{15}N spectra to $^{15}NH_4Cl$ and then converted to nitromethane scale by using the following relationship: $d\{^{15}\text{N(nitromethane)}\} = d\{^{15}\text{N(ammonium chloride)}\} - 338.1$ ppm.

X-ray Crystallography. Suitable crystals were obtained by slow evaporation of a methanol solution. The data collection was carried out, at $T = 150$ K, on a diffractometer equipped with molybdenum Kα radiation, a graphite monochromator, and an crystal cooling device. Crystal data: monoclinic *Cc*, $Z = 4$, $a = 4.4700(6)$ Å, $b = 23.896(3)$ Å, $c = 9.3400(13)$ Å, and $\beta = 99.376(7)°$, $V = 984.3(2)$Å^3. Structure solution was carried

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out with use of direct methods SIR97,[19] and the least-squares refinement was performed in SHELXL97[20] with F^2 magnitudes.

Computational Details. The optimization of the structures of all compounds discussed in this paper was carried out at the B3LYP/6-311++G** level,[21,22] using the facilities of the Gaussian 98 set of programs.[23] Absolute shielding σ were calculated, at the same level, over these geometries within the GIAO approximation.[24,25]

Acknowledgment. Financial support was provided by the Spanish DGICYT (Project Nos. BQU-2000-0252 and BQU-2000-0906). Dr. Roberto Sastre (CSIC, Madrid) helped us with the electronic spectra at low temperatures. L.I. acknowledges the "Ministerio de Educacion y Cultura" of Spain for a postdoctoral fellowship.

Supporting Information Available: Crystallographic information for **2a** (CIF file)and computational results (total energy and geometry) optimized at the B3LYP/6-311++G** level. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034833U

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