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Theoretical anharmonic Raman and infrared spectra with vibrational assignments and NBO analysis for 1-methyl-4-nitropyrazole

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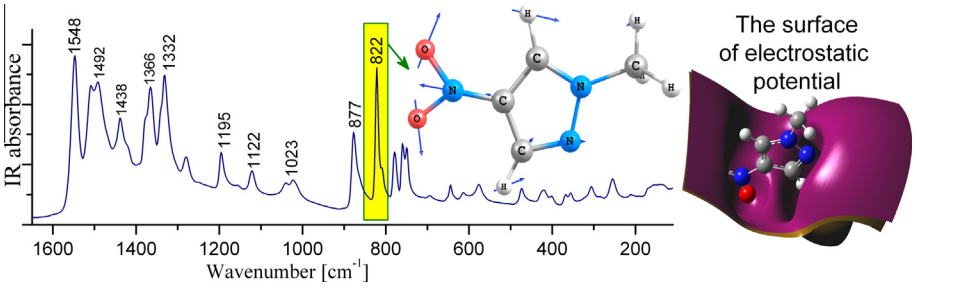
HIGHLIGHTS

- Comprehensive PED assignment for 1-methyl-4-nitropyrazole is reported.
- IR, Raman, ^{1}H NMR, ^{1}H–^{1}H NMR and ^{13}C NMR and cyclic voltamperometry methods are used.
- The fully anharmonic IR and Raman spectra are presented for the first time.
- Detailed NBO analysis has been done in order to explain the stabilizing interaction.
- The stability arising from hyper conjugative interaction is demonstrated.

GRAPHICAL ABSTRACT



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ABSTRACT

Both experimental and calculated spectral and electronic properties of 1-methyl-4-nitropyrazole have been demonstrated. Experimental values have been compared with theoretical computations and also new hybrid density functionals, APF (Austin–Petersson–Frisch) and APF(D), have been tested and compared to B3LYP hybrid functional. The theoretical wavenumbers of fully anharmonic infrared and Raman spectra with anharmonic intensities of 1-methyl-4-nitropyrazole are in very good agreement with the experimental observations. The detailed interpretation of the infrared and Raman spectra is reported based on potential energy distribution (PED). The ring N1—N2 bond distance of 1-methyl-4-nitropyrazole, calculated with both APF/6-311++G(*df*,*pd*) and APF-D/6-311++G(*df*,*pd*) models, is much underestimated in comparison with X-ray experimental value. Overall results point that B3LYP functional with 6-311++G(*df*,*pd*) basis function better predicts the bond lengths and angles of titled compound than both APF and APF-D ones. As a key factor for biological activity of nitro compounds, the redox potential of 1-methyl-4-nitropyrazole in water solution was also measured and then was set against the calculated electronic properties. The analysis of the calculated components of HOMO and LUMO orbitals has shown that nitrogen and oxygen atoms of nitro group are the most probable site of acceptance of electron. Hence, nitro group should be the most sensitive fragment of 1-methyl-4-nitropyrazole molecule to the reduction process. Moreover, the stability of the 1-methyl-4-nitropyrazole arising from hyper conjugative interactions has been studied using natural bond orbital (NBO) analysis. Unambiguous assignment of values of proton chemical shifts to appropriate protons has been finally made thanks to two dimensional (2D) ^{1}H–^{1}H NMR spectroscopy.

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1. Introduction

Research on compounds designed to act specifically on tumor cells have recently attracted the attention of medicinal chemists. Sophisticated concept of targeting hypoxic tumor cells consists in use of prodrug which is susceptible for bioreduction. This action should increase effectiveness of treatment and decrease undesired side effects of cancer chemotherapy. Amongst the other potentially bioreductive organic compounds, the nitro compounds have been most extensively applied in medicine against protozoal and anaerobic infections [1] and in cancer therapy as radiosensitizers or molecular cytotoxins [2,3]. Biological activity of these compounds is strictly connected with reduction of nitro group which can accept up to six electrons producing primary amine – usually the final biologically active form of the drug. Nitroheterocyclic moiety as a part of drug molecule is potentially able to break DNA strand during reduction and can destabilize its helix, causing molecular damages similar to those produced by free radicals [2]. Recently, we have synthesized and biologically tested several platinum complexes with nitroheterocycles as ligands. During our research and tests we have found that trans-dichlorobis(1-methyl-4-nitropyrazole)platinum(II), significantly outperforms reference drug Cisplatin in cytostatic properties *in vitro* [4]. This work is a part of investigation into the properties of this compound and will help to describe its spectroscopic and electrochemical properties by computational quantum methods in order to use them in rational design of this class of bioreductive antitumor drugs. Thus, the main goal of this work is fine approximation of vibrational spectra of 1-methyl-4-nitropyrazole and Natural Bond Orbital analysis associated with forecasting properties of title compound.

2. Experimental details

The Attenuated Total Reflectance IR (ATR-FT-IR) spectrum (4000–450 cm^{-1}) of 1-methyl-4-nitropyrazole was measured with the Perkin–Elmer Spectrum Two UATR spectrophotometer using clean pulverized crystals of compound (on the diamond crystal surface, 8 scans, resolution: 1 cm^{-1}). The FIR range below 450 cm^{-1} was recorded on the Bruker Vertex 70v FT-IR spectrometer with this same resolution (detector: DTGS – deuterated triglycine sulfate, Beamsplitter: Mylar multilayer). The Raman spectrum of crystalline powders was recorded in the range of 3600–50 cm^{-1} with a 2 cm^{-1} spectral resolution on the Bruker MultiRAM FT-Raman spectrometer equipped with a Nd:YAG laser (emitting at 1064 nm) and a germanium detector cooled with liquid nitrogen. Spectra of samples were collected with laser power of 500 mW and 1024 scans. ^{1}H NMR (300.14 MHz), 2D ^{1}H–^{1}H NMR (300.14 MHz) and ^{13}C NMR spectra (broadband full decoupling method: 75.47 MHz), 5 mm tubes, concentration 20 mg of compound in 0.6 mL of solvent (≈0.1 M solution), Bruker Fourier spectrometer (Bruker, Rheinstetten, Germany). Thin-layer chromatography method (TLC) was applied to monitor the reaction progress as well as to confirm the purity of the synthesized compound. TLC–PET foils with fluorescent indicator 254 nm, silica gel matrix plates (Fluka) for TLC were used, eluting medium was chloroform–acetone (9:1), detection of the compounds on the chromatograms was done with UV light and/or by treatment with iodine vapors. The melting point of 1-methyl-4-nitropyrazole was measured on the Büchi 510 and Büchi M560 melting point apparatuses (BÜCHI Labortechnik AG, CH-9230 Flawil/SG, Switzerland) and was uncorrected.

The potential of reduction/oxidation of 1-methyl-4-nitropyrazole was established using cyclic voltamperometry method with Autolab PGSTAT12. Dropping mercury electrode was used as working electrode and silver chloride electrode as an internal reference. The measurement was carried out at 25 °C in 0.1 M NaCl solution of tested compound saturated with nitrogen.

2.1. Synthesis of 1-methyl-4-nitropyrazole

1-Methyl-4-nitropyrazole, used in experiments, was obtained by thermal decarboxylation of 1-methyl-4-nitro-3 or 5-pyrazolecarboxylic acid to avoid its contamination by the other nitro isomers which could be created during direct nitration of 1-methylpyrazole [5] and finally purified with column chromatography with silica gel (eluent: chloroform–acetone 9:1 mixture). M.p. = 90 °C (Ref. 90–91 °C [6]).

^{1}H NMR of 1-methyl-4-nitropyrazole: ($CDCl_3$, Bruker, 300.15 MHz): δ 3.97 (s; 3H, —C**H₃**), 8.05 (s; 1H, proton at position 3 of pyrazole ring), 8.12 (s; 1H, proton at position 5 of pyrazole ring) ppm.

^{1}H–^{1}H 2D NMR–COSY (Correlation Spectroscopy) ($CDCl_3$, Bruker, 300.15 MHz) shows weak coupling between protons of methyl group (3.97 ppm) and proton at position 5 of pyrazole ring. (8.12 ppm), what proves that this proton at position 5, which is in closer distance to protons of methyl group than proton at position 3, has just chemical shift value which is equalled 8.12 ppm.

^{13}C NMR of 1-methyl-4-nitropyrazole: ($CDCl_3$, Bruker, 75.47 MHz): δ 40.3 (=N—**C**H_3), 129.2 (C5), 136.0 (C4 and C3) ppm.

3. Computational details

A full geometry optimization has been performed using the B3LYP [5,7,8] and APF(D) [9] hybrid density functionals with the extended 6-311++G(*df*,*pd*) basis set. This is the valence triple-zeta basis set, augmented by *d*,*f*-polarization functions on C, N, and O atoms, *p*,*d*-polarization functions on H atoms and enlarged by diffuse functions on all atoms [10,11]. Subsequently, harmonic and anharmonic vibrational frequencies with infrared intensities, Raman scattering activities, and natural population analysis were computed at the same level of theory. All computations were carried out with the Gaussian 09 rev. D.01 [12]. It should be noted that this revision of Gaussian package gives new possibility of compute fully anharmonic IR intensities for the fundamentals, overtones and combination bands [13]. Natural bond orbital (NBO) analysis was performed and atomic charges were calculated by using the NBO 5.0 stand-alone program [14,15]. The normal coordinate analyses were performed, as described previously [16–20]. The non redundant set of 36 internal coordinates was defined as recommended by Fogarasi and Pulay [21]. The force constants matrix was transformed from Cartesian coordinates to the internal coordinates and potential energy distribution (PED) matrix was calculated [22]. Description of internal coordinates and atom numbering are shown in Table 1 and Fig. 1. Five harmonic frequencies which correspond to the CH stretching vibrations were scaled by a factor of 0.958, while the remaining thirty one harmonic frequencies, below 2000 cm^{-1}, were scaled by 0.983. These scaling factors were successfully used in our previous theoretical study on aniline [16], substituted-anilines [18–20] and 5-bromo-2-nitropyridine [17] and well correlated with data obtained by anharmonic approximation [23–26].

The Raman activities S_i^R calculated with Gaussian 09 package are converted to relative Raman intensities I^R using the following relationship delivered from the intensity theory of Raman scattering [27]:

$$I_i^R = \frac{f(v_0 - v_i)^4 \cdot S_i^R}{v_i\left(1 - exp\left(-\frac{h \cdot c \cdot v_i}{k \cdot T}\right)\right)} \quad (1)$$

where v_i is the calculated anharmonic frequency (cm^{-1}) of *i*th normal mode, S_i^R is the Raman scattering activity; *h*, *k*, *c*, and *T* are