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Synthesis, molecular structure, spectroscopic properties and stability of (*Z*)-*N*-methyl-*C*-2,4,6-trimethylphenylnitrone

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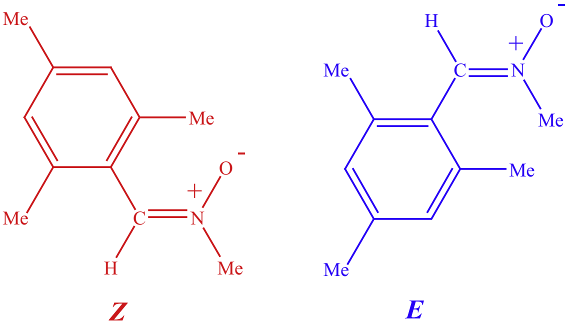
HIGHLIGHTS

- New *N*-methyl-*C*-2,4,6-trimethylphenylnitrone has been synthesized.
- *Z*-isomer is more stable than the *E*-one both in gas phase and in solution.
- The IR, electronic and NMR spectra were studied experimentally and theoretically.
- The studied nitrone has about five times higher NLO than urea.
- NBO analysis indicates the presence of weak C—H- - -O non-conventional interaction.

GRAPHICAL ABSTRACT

New *N*-methyl-*C*-2,4,6-trimethylphenylnitrone has been synthesized and characterized using FTIR, NMR, UV–Vis, high resolution mass spectrometry and X-ray diffraction. The relative stability and percentage population of its two possible isomers (*E* and *Z*) have been calculated using the B3LYP/6-311++G(d,p).



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This paper is dedicated to our wonderful friend Dr. Samir Senior from Alexandria University (Egypt) who recently passed away.

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ABSTRACT

New *N*-methyl-*C*-2,4,6-trimethylphenylnitrone **1** has been synthesized starting from N-methylhydroxylamine and mesitaldehyde. The product was fully characterized using different spectroscopic techniques; FTIR, NMR, UV–Vis, high resolution mass spectrometry and X-ray diffraction. The relative stability and percent of population of its two possible isomers (*E* and *Z*) were calculated using the B3LYP/6-311++G(d,p) method in gas phase and in solution. In agreement with the X-ray results, it was found that *Z*-isomer is the most stable one in both gas phase and solution. The molecular geometry, vibrational frequencies, gauge-including atomic orbital (GIAO), and chemical shift values were also calculated using the same level of theory. The TD-DFT results of the studied nitrone predicted a π–π^* transition band at 285.1 nm ($f_{osc} = 0.3543$) in the gas phase. The rest of the spectral bands undergo either hyperchromic or hypsochromic shifts in the presence of solvent. Polarizability and HOMO–LUMO gap values were used to predict the nonlinear optical properties (NLO) of the studied compound. NBO analysis has been used to determine the most accurate Lewis structure of the studied molecule.

Introduction

Nitrones, whose name comes from nitrogen ketone, have been widely reviewed and illustrated in synthetic chemistry [1,2].

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Nitrone derivatives have been used for the synthesis of many natural products of biological interesting materials [3]. These compounds were found to act as an important key step in the efficient incorporation of multiple stereocenters *via* cycloaddition reactions [4]. The nitrone moiety has possessed pharmacological activity that provides the effective center in the molecular structure of many drugs [5]. This makes nitrones a potential candidates in many experimental animal models as biological active materials [6,7] and as anti-cancer drugs [8]. A combination of nitrones and anti-oxidants was found to have a synergistic effect to prevent the acute acoustic noise-induced hearing loss [9]. The corrosion of metals and alloys in organic acidic media was significantly lowered when treated by nitrones [10–13].

Inouye et al. [14] proposed that crystalline nitrones exist as mainly *Z*-isomer. They also found that the *E*/*Z* isomerization occurred when it dissolved. There are only few publications that deal with the theoretical studies on the molecular structure and spectral properties of nitrones [15,16].

In this work, the new *N*-methyl-*C*-2,4,6-trimethylphenylnitrone **1** is synthesized and characterized using FTIR, ^{1}H, ^{13}C NMR, mass spectrometry and X-ray diffraction. We have studied the equilibrium between the *E* and *Z* isomers in gas phase and in various solvents (with different polarity) to predict the effect of solvent on the vibrational, electronic, and NMR spectra of the most stable isomer. Frontier molecular orbitals (FMOs) and natural atomic charges were calculated at the same level of theory. Natural bond orbital (NBO) calculations were performed to predict the most accurate Lewis structure of the studied nitrone. Also, the stabilization energy of various intramolecular interactions was investigated.

Experimental section

Material and instrumentation

All solvents and reagents were obtained from Sigma–Aldrich and were used as received. ^{1}H and ^{13}C NMR spectra (in $CDCl_3$) were measured on Bruker Avance III HD 600 MHz (Ascend™ Magnet) spectrometer at ambient temperature. ^{1}H and ^{13}C chemical shifts (δ) are expressed in ppm relative to $Si(Me)_4$. Infrared spectra (400–4000 cm^{-1}) were recorded on an Alpha Bruker FT-IR instrument in KBr pellets. Mass spectra were carried out using high resolution ion-trap time-of-flight mass spectrometry interfaced with electrospray source (MicrOTOF II mass spectrometry from Bruker). The drying gas temperature of the mass spectrometry was maintained at 200 °C. N_2 was used as nebulizer gas at a pressure of 20 psi. Positive mode scanning was performed at the range of *m*/*z* 50–1500. Acetonitrile solution of the product compound (nitrone) was continuously introduced into the mass spectrometer detector with a syringe pump at a flow rate of 20 μL/min. The electrospray voltage and the collision cell RF were set at 2.5 kV and 100 Vpp, respectively. Tandem mass spectrometry was applied to the trapped peak at *m*/*z* 178.1233 with collision energy (CID) set at 35 eV. The accuracy of the mass spectrometer was enough to assign the fragmentation species as good as 5 ppm as shown in Fig. S1 (Supplementary Information). Liquid chromatography (Agilinet series 1260) was used to separate and measure the UV/Vis spectrum for the nitrone compound in aqueous medium. Five microliter of acetonitrile solution (1 mg of nitrone/mL) was introduced into HPLC instrument that is coupled with UV/Vis detector. Acetonitrile/water mixture (30:70) was used as mobile phase at a flow rate of 1.0 mL/min for 2 min. After that, the mixture was set at 100% water for another 10 min. Full scan UV/Vis spectrum was measured for the separated nitrone peak at retention time = 3.8 min, which means that the spectrum was recorded in 100% water.

Synthesis of (Z)-N-methyl-C-2,4,6-trimethylphenylnitrone **1**

Sodium carbonate (0.63 g, 5.98 mmol) was added to a solution of N-methylhydroxylamine hydrochloride (1.00 g, 11.97 mmol) in

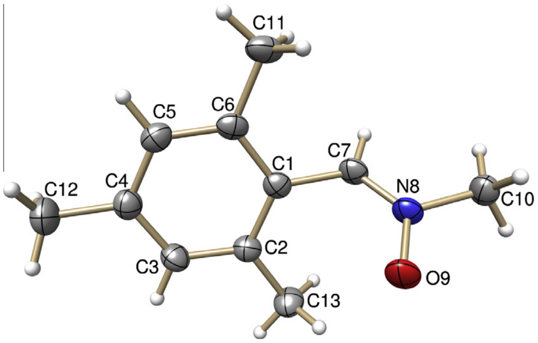


Fig. 1. Thermal ellipsoid plot of **1**. The thermal ellipsoids are drawn at 50% probability.

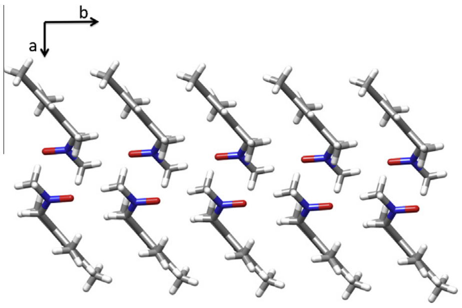
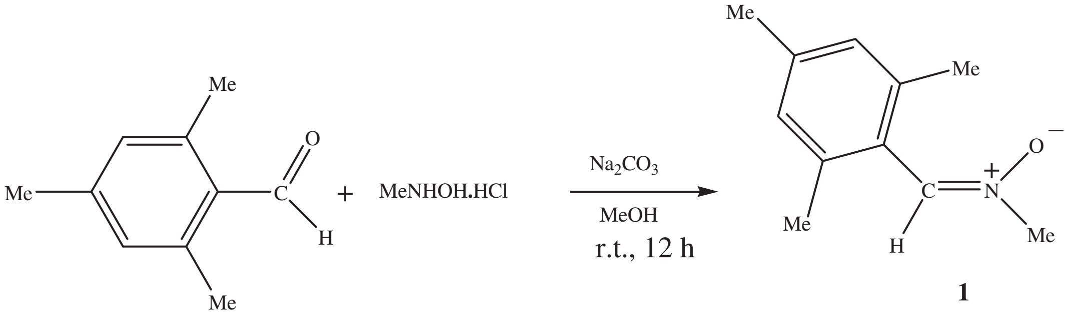


Fig. 2. Packing of **1** viewed along crystallographic *c*-axis.



Scheme 1. Synthesis of acyclic nitrone **1**.