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A combined experimental and theoretical study of the tautomeric and conformational properties of (5-phenyl-tetrazol-2-yl)-acetic acid methyl ester

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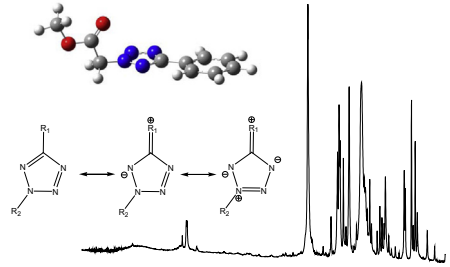
HIGHLIGHTS

- X-ray crystal structure was determined for novel tetrazole species.
- Electronic delocalization interactions are promoted by the nitrogen lone pair.
- Two conformations are almost isoenergetic, depending on the orientation of the C=O with respect to the tetrazole ring.
- The tetrazol-2-tautomer is more stable than the tetrazol-1-form.
- Vibrational properties are investigated.

GRAPHICAL ABSTRACT



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ABSTRACT

The tautomeric and conformational properties of a new tetrazole derivative are studied in a combined approach that includes the analysis of the experimental vibrational data together with theoretical calculation methods, especially in terms of natural bond orbital (NBO) population analysis. Moreover, the molecular and crystal structure was determined by single crystal X-ray diffraction. The compound crystallized as the 2-tautomeric form, monoclinic space group $P2_1/c$ with $Z = 4$, $a = 10.0630(14)$, $b = 8.2879(11)$, $c = 12.8375(18)$ Å, $\beta = 105.546(3)°$, $V = 1031.5(2)$ Å^3. The tetrazole and phenyl rings are coplanar with the acetate group oriented perpendicular to the plane. The NBO analysis showed that delocalizing interactions of the lp_p(N2) lone pair orbital contributes to a strong resonance interactions with both adjacent π^*(N3=N4) and π^*(N1=C5) antibonding orbitals of the tetrazole group.

Introduction

Tetrazoles are a class of synthetic heterocycles with a wide range of applications in organic chemistry [1], coordination chemistry [2], the photographic industry and medicinal chemistry [3], as well as activators in oligonucleotide synthesis [4]. The 5-substituted tetrazoles are the non-classical bioisosteres of carboxylic acids [5], possessing similar acidities but higher lipophilicities and metabolic resistance [6]. In addition, the 5-phenyltetrazoles are known to exhibit several biological activities including antibacterial, antifungal [7], antinociceptive [8], analgesic and anti-inflammatory [9], anticonvulsant [10], hypoglycemic [11], and antihypertensive activities [12].

The thermal decomposition of tetrazole has also gained attention [13] mostly with the development of high-energy

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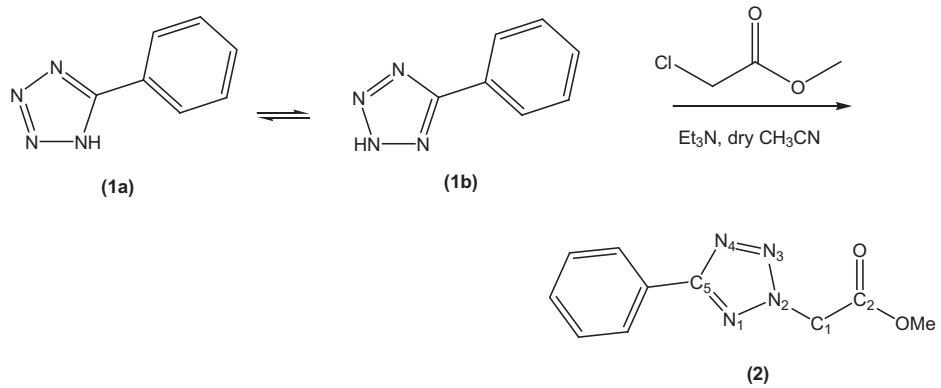

Scheme 1. Synthetic route of the title compound. Relevant atom numbering is also defined.

tetrazole-based compounds as potential explosive materials, electric igniters and solid rocket propellant formulations [14]. The explosive properties of tetrazoles are related to their molecular and electronic structure, the ranking in explosive behavior of 5-substituted tetrazoles correlates with the electron withdrawing capacity of the substituents [15].

From the structural point of view, it is well-known that the tetrazole cycle exists in two tautomeric forms, differing by position of the hydrogen atom [16]. Experimental techniques [17–19] and theoretical approaches [20–22] were applied to the study of this equilibrium. Further 1- and 2-substitution of the tetrazole hydrogen by organic group is also feasible, giving access to a variety of 1- and 2-substituted tetrazole species.

In this work a new derivative was synthesized by the base catalyzed esterification of 5-phenyl-2*H*-1,2,3,4-tetrazole (**1**) with methyl 2-chloroacetate (Scheme 1), using the reaction conditions established earlier [23]. The precursor compound (**1**) as well as N-(R-aminoalkyl)tetrazoles are known to exist in solution as equilibrium mixtures of N1 (**1a**) and N2 (**1b**) tautomers. The position of equilibrium depends considerably on the polarity of the solvent and the nature of substituents on the tetrazole ring. The use of triethylamine and acetonitrile followed by recrystallization from *n*-hexane exclusively affords a single pure tautomer [24]. Thus, following this procedure, the hitherto unknown (5-phenyl-tetrazol-2-yl)-acetic acid methyl ester (**2**) species has been prepared.

The crystal structure and vibrational properties were determined by single crystal X-ray diffraction and infrared spectroscopy complemented by quantum chemical calculations at the B3LYP/6-311++G(d,p) level of approximation. Moreover, the natural bond orbital (NBO) population analyses were determined to understand the effect of electronic interactions in the structural and conformational properties of the tetrazole moiety.

Experimental

Synthesis of (5-phenyl-tetrazol-2-yl)-acetic acid methyl ester

A mixture of 5-phenyltetrazole (3 mmol), triethylamine (12 mmol) and acetonitrile (25 mL) was added dropwise to a stirred solution of methyl chloroacetate (6 mmol) in 15 mL of acetonitrile. The reaction mixture was heated in an oil bath for 2 h keeping the temperature at 82 °C. The progress of the reaction was monitored by TLC. Acetonitrile was removed under reduced pressure and product was re-crystallized in *n*-hexane to get pure (5-phenyl-tetrazol-2-yl)-acetic acid methyl ester as a white crystalline solid (yield: 73%). mp. 98–100 °C. IR (Neat) cm^{-1}: 1281 (N=N–N), 1547 (Ar–C=C), 1606 (C=N), 1756 (C=O), 2854 (CH_3), 3067 (Ar–C–H); ^{1}H NMR (300 MHz, DMSO) δ (ppm): 3.75 (s, 2H, CH_3), 5.93 (s, 2H, CH_2), 7.57 (m, 3H, Ar–$H_{m,p}$), 8.08 (m, 2H, Ar–H_o). ^{13}C NMR (75 MHz, DMSO) δ (ppm): 53.43, 53.83 ($\underline{CH_2}$C=O, OCH_3), 126.8 (1′C), 127.0 (2′C), 129.8 (3′C), 131.3 (4′C), 164.9 (tetrazole ring carbon), 167.1 (C=O).

The precursor 5-phenyl tetrazole was prepared according to the literature procedure [6] (yield: 78%). mp 216 °C (lit. [6] 217 °C). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 7.59–7.62 (m, 3H, Ar–H), 8.02–8.06 (m, 2H, Ar–H), ^{13}C NMR (75 MHz, DMSO) δ (ppm): 124.6 (1′C), 127.2 (2′C), 129.9 (3′C) 131.7 (4′C), 155.8 (tetrazole ring carbon).

Crystal structure determination

Colorless crystal, size 0.37 × 0.22 × 0.20 mm^3, monoclinic space group $P2_1/c$ with $Z = 4$, $a = 10.0630(14)$, $b = 8.2879(11)$, $c = 12.8375(18)$ Å, $\beta = 105.546(3)°$, $V = 1031.5(2)$ $Å^3$; $D_c = 1.405$ Mg/m^3, $\mu = 0.103$ mm^{-1}, $F(000) = 456$. The intensity data were recorded using a Bruker SMART CCD area-detector diffractometer with graphite monochromated MoK_α radiation ($\lambda = 0.71073$ Å) at $T = 130(2)$ K. 9446 reflections collected $2.1 > \Theta > 27.9°$; 2466 independent reflections $I > 2\sigma(I)$. Structure solution by direct method full-matrix least squares refinement [25] based on F^2 and 146 parameters. All but H-atoms were refined anisotropically, hydrogen atoms were clearly located from difference Fourier maps, refined at idealized positions riding on the carbon or nitrogen atoms with isotropic displacement parameters $U_{iso}(H) = 1.2U_{eq}(C)$ or $1.5U_{eq}(C_{methyl})$ and C–H 0.95–0.99 Å. Refinement converged at R1 = 0.039 [$I > 2\sigma(I)$], wR2 = 0.100 [all data] and $S = 1.049$; min/-max ΔF −0.20/0.27 e/$Å^3$.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-1015473. Copies of available material can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or contacting the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. Crystal data, structure refinements and geometrical parameters are given as Supplementary material.

Instrumentation

Melting point was determined using a digital Gallenkamp (SANYO) model MPDBM3.5 apparatus and is uncorrected. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ with a 300 MHz Bruker AM-300 spectrophotometer. Mass Spectra (EI, 70 eV) were taken on a GC–MS, Agilent technologies 6890N with