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Crystallographic and conformational analysis of 2-methyl-3-(2-nitro-phenyl)-4-phenyl-[1,2,4]oxadiazolidin-5-one

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Molecular and crystal structure of 2-methyl-3-(2-nitro-phenyl)-4-phenyl-[1,2,4]oxadiazolidin-5-one, $C_{15}H_{13}N_3O_4$, have been determined by single crystal X-ray diffraction study. The title compound is monoclinic, with $a = 10.0313(8)$ Å, $b = 9.0372(5)$ Å, $c = 15.5964(14)$ Å, $\beta = 96.926(7)^\circ$, $Z = 4$, $D_x = 1.42$ g/cm³, μ (Mo- K_α) = 0.105 mm⁻¹, and space group is $P 2_1/c$. The structure was solved by direct methods and refined to a final $R = 0.036$ for 1894 reflections with $I > 4\sigma(I)$. The crystal structure is stabilized by C—H...O type inter-molecular, C—H...N and C—H...O type intra-molecular, π – π stacking and edge to face (C—H... π -ring) interactions. To enlighten conformational flexibility of the title molecule, selected two torsion angles are varied from -180° to $+180^\circ$ in every 10° separately and then molecular energy profile is calculated and construed.

KEY WORDS: Crystal structure; nitrones; AM1; conformational analysis.

Introduction

The nitrones are well-known 1,3-dipoles in thermal cycloaddition reactions with a wide variety of carbon–carbon, carbon–nitrogen, carbon–sulphur and nitrogen–phosphorus multiple bond systems to provide various heterocyclic five-membered ring systems.^{1–4} The cycloadducts of di- and triarylimidazoline 3-oxides^{5–7} with variety of dipolarophiles^{8–13} give bicyclic compounds with interesting biological activity. For instance, a series of tetrahydroimidazo compounds

including tetrahydroimidazooxadiazolones were tested for their anticancer activity and found to be quite active at 10^{-5} molar concentrations. On the other hand, they are a source of new heterocyclic compounds via interesting ring-opening reactions.^{14,15} The reaction of imidazoline 3-oxides with aryl isocyanates was shown to proceed regio and diastereoselectively. Interesting reactions of this adducts at different conditions especially the double *cis* elimination they undergo in the presence of dialkylamines was reported.^{14,15}

Here we report the molecular and crystal structure of 2-methyl-3-(2-nitro-phenyl)-4-phenyl-[1,2,4]oxadiazolidin-5-one, determined by single crystal X-ray diffraction study, and the conformational analysis of the title molecule with respect to two selected torsion angles is achieved by AM1 semi-empirical quantum mechanical model.

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Experimental

The title compound was prepared and isolated as follows: to the solution of nitrone (1 mmol) in acetonitrile (13 mL) phenyl isocyanate (3 mmol) dissolved in the same solvent (2 mL) was added and the reaction mixture refluxed for 24 h. The solvent was evaporated and the product crystallized from ethanol. A suitable sample of size 0.25 mm × 0.19 mm × 0.11 mm was selected for the crystallographic study. All diffraction measurements were performed at room temperature (293 K) using graphite monochromated Mo-K α radiation and an STOE IPDS II diffractometer. The systematic absences and intensity symmetries indicated the monoclinic $P 2_1/c$ space group. A total of 19991 intensities with $\theta_{\max} = 25.99^\circ$ were collected in the rotation mode. The intensities were corrected for Lorentz and polarization factors, but not for absorption correction ($\mu = 0.105 \text{ mm}^{-1}$).

The structure was solved by direct methods using SHELXS-97.¹⁶ The refinement was carried out by full-matrix least-squares method on the positional and anisotropic temperature parameters of the non-hydrogen atoms, or equivalently corresponding to 252 crystallographic parameters. The structure was refined to $R_1 = 0.044$ for observed reflections which obeyed to the condition of $1894 F_0 > 4\sigma(F_0)$ and to $R_1 = 0.076$ for all 2521 data used in refinement process. The maximum peaks and deepest hole observed in the final $\Delta\rho$ map were 0.22 and $-0.14 \text{ e}\text{\AA}^{-3}$, respectively. The scattering factors were taken from SHELXL-97.¹⁶ The data collection conditions and parameters of refinement process are listed in Table 1.

The geometry optimization of the molecule leading to energy minima was achieved by using AM1 self-consistent field molecular orbital¹⁷ method at the restricted Hartree–Fock (RHF) level.¹⁸ The optimization was performed by Polak–Ribiere conjugate gradient method, RMS gradient of $0.001 \text{ kcal}/\text{\AA} \text{ mol}$ and convergence criteria of 0.01 kcal/mol . To elucidate conformational flexibility of the title molecule, two selected torsion angles [T1(C10–C9–C2–N1)

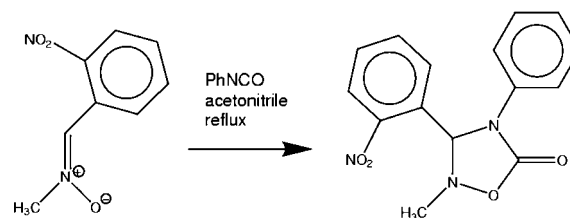
Table 1. Crystallographic Data for the Title Compound

CCDC deposit no.	256670
Color/shape	Colorless/needle
Chemical formula	C ₁₅ H ₁₃ N ₃ O ₄
Formula weight	299.28
Temperature (K)	293(2)
Crystal system	Monoclinic
Space group	$P 2_1/c$
Unit cell dimensions	
a (Å)	10.0313(8)
b (Å)	9.0372(5)
c (Å)	15.5964(14)
β (°)	96.926(7)
Volume (Å ³)	1403.57(19)
Z	4
Density (calculated) (g/cm ³)	1.416
Absorption coefficient (mm ⁻¹)	0.105
Calculated T_{\min} , T_{\max}	0.976, 0.989
Diffractometer/meas. meth.	STOE IPDS II/rotation
θ range for data collection (°)	2.05–25.99
Unique reflections measured	2521
Independent/observed reflections	2521/1894
Data/restraints/parameters	2521/0/252
Extinction coefficient	0.021(2)
Goodness of fit on F^2	1.092
Final R indices [$I > 4\sigma(I)$]	$R_1 = 0.044$, $wR_2 = 0.093$
R indices (all data)	$R_1 = 0.076$, $wR_2 = 0.107$

and T2(C8–C3–N1–C2)] are varied from -180° to $+180^\circ$ in every 10° and molecular energy profile is obtained by performing single-point calculations on the calculated potential energy surface.

Results and discussion

An ORTEP III diagram with the atom-numbering scheme and molecular packing drawing with inter-molecular weak interactions in the



Scheme 1. Synthesis scheme for preparation of the title compound.

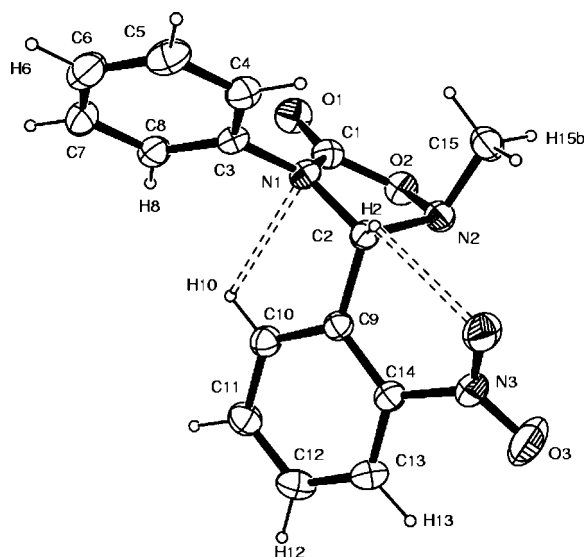


Fig. 1. An ORTEP III view of the title molecule with the atomic numbering scheme showing intra-molecular weak interactions, which are depicted by dashed lines. Displacement ellipsoids are shown at the 30% probability level.

unit cell for the title compound are shown in Fig. 1 and Fig. 2, respectively. Comparative results obtained from X-ray crystallographic and computational studies are presented in Table 2.

The angle between the average plane of the nitro group and average ring plane to which the nitro group links is $26.8(3)^\circ$. The angle between phenyl and 2-nitro phenyl ring (R2) is $54.82(9)^\circ$. The C3...C8 phenyl ring (R1) makes dihedral angle of $56.34(7)^\circ$ with the average plane of five-membered heterocyclic ring. The average plane throughout five-membered heterocyclic ring is nearly perpendicular to 2-nitro phenyl ring with the angle of $85.30(6)^\circ$. The bond distance of C1—O1 and the bond angles of O1—C1—N1, O1—C1—O2 and N1—C1—O2 are in agreement with those of previous studies^{20–23} in the literature. Atom N2 has maximum deviation with $0.187(1)$ Å from average ring plane of five-membered heterocyclic ring. [1,2,4]Oxadiazolidin ring of which weighted average ring bond distance is 1.4256 Å is adopted to twisted conformation on N2—C2 bond. The dihedral angle between the least-square planes defined by N1, N2, C2 atoms and N2, O2, C1, N1 atoms is $29.00(9)^\circ$. Atoms N2 and C2 have respective deviations of $0.187(2)$ Å and $-0.174(2)$ Å from the average ring plane of the five-membered heterocyclic ring. Atom C2 that is member of the

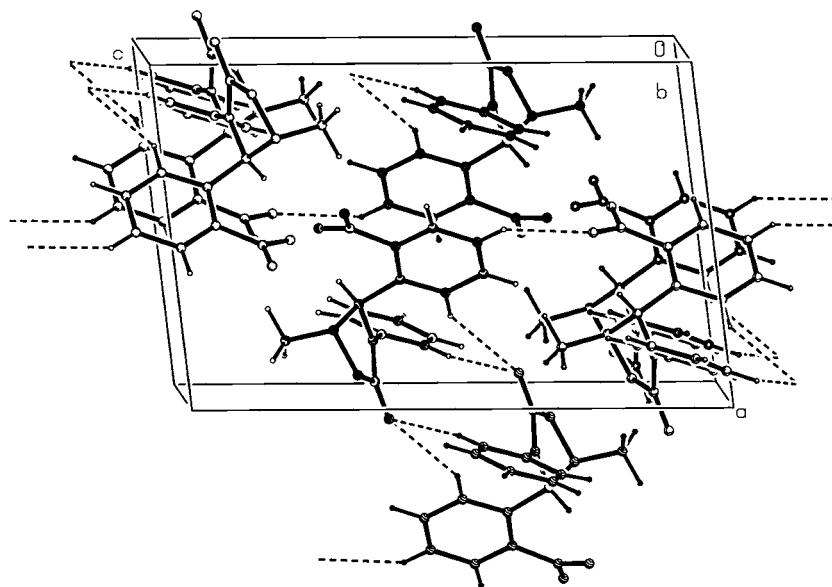


Fig. 2. Unit-cell contents with the hydrogen-bonding scheme indicated by dashed lines.

Table 2. Comparison of the Selected Bond Lengths (Å), Bond and Torsion Angles (°)

	X-ray	AM1
Bond lengths		
N1–C2	1.453(2)	1.482
N1–C3	1.429(2)	1.413
N1–C1	1.354(2)	1.415
O2–N2	1.469(2)	1.367
O2–C1	1.375(2)	1.410
N3–O3	1.209(2)	1.201
N2–C2	1.476(2)	1.528
O1–C1	1.200(2)	1.225
Bond angles		
O3–N3–O4	122.19(16)	121.43
C1–O2–N2	108.27(11)	112.26
C1–N1–C2	109.80(13)	106.61
O1–C1–N1	129.90(16)	133.74
O1–C1–O2	122.14(15)	116.95
N1–C1–O2	107.94(13)	109.14
N1–C2–N2	102.28(12)	105.56
N1–C2–C9	112.76(12)	113.17
Torsion angle		
C1–O2–N2–C2	28.98(15)	10.35
N2–O2–C1–O1	166.38(15)	177.73
C1–N1–C2–N2	24.67(15)	6.79
Torsion angle		
C2–N1–C1–O2	–6.78(17)	–0.89
N2–O2–C1–N1	–14.53(17)	–6.33
O2–N2–C2–N1	–31.01(13)	–10.37

heterocyclic ring has R-chiral configuration. The substituents of the five-membered ring have different stereo-chemical configurations. Although the methyl and 2-nitro-phenyl group are linked pseudo-axially, phenyl ring is linked pseudo-equatorially to the five-membered heterocyclic ring. As different from all other substituents of five-membered ring, atom H2 has bisectonal (neither pseudo-equatorial nor pseudo-axial) pseudo-stereochemical configuration.

The crystal structure is stabilized by inter- and intra-molecular interactions of which details are given in Table 3, in addition to π – π stacking and edge to face (C–H... π -ring) interactions. One of the inter-molecular weak interactions, C8–H8...O1, is almost linear with the angle of 171.1°. There are two remarkable π – π stacking interactions relating to the R1 ring [fractional centroid coordinates: 0.82864(8), 0.35722(8),

0.09345(6), Cg(2)] and R2 ring [fractional centroid coordinates: 0.59388(7), –0.18392(8), 0.00169(5), Cg(3)] in the crystal structure. The perpendicular distances of these π – π stacking interactions (R1–R2 and R2–R2) are found as 3.188 Å, 3.672 Å, and their symmetry codes are [x, y, z], and [1 – x, –y, –z], respectively. Since these perpendicular distances between the interacting π -rings are smaller than 3.8 Å, it can be stated that both stacking interactions supply considerable contributions to stabilization of the crystal structure. Additionally, three edge to face (X–H...Cg(π -ring)) interactions relating to the R1 and R2 rings are observed in the structure. Perpendicular distances H...(π -ring) for the interactions of C6–H6...Cg(3), C13–H13...Cg(2) and C15–H15B...Cg(2) are found as 2.905, 2.811 and 2.942 Å with the respective symmetry codes; [x, 1 + y, z], [1 – x, –y, –z] and [2 – x, –1/2 + y, 1/2 – z].

According to crystallographic study, T1(C10–C9–C2–N1) and T2(C8–C3–N1–C2) are obtained as 0.5(2)° and 120.82(17)°, whereas these torsion angles are 15.1514° and 155.573° in the optimized molecular structure. Another remarkable differentiation from the crystallographic study is observed in conformation of the five-membered ring (see Table 2). The results from computational study suggests that the five-membered ring is nearly adopted in planar conformation. AM1, which is a semi empirical method, can not represent structural properties of the crystalline materials

Table 3. Hydrogen Bonding Geometry (Å, °) for the Title Compound

D–H...A	D–H	H...A	D...A	\angle D–H...A
C8–H8...O1 ^a	0.956	2.586	3.533	171.1
C10–H10...O1 ^a	0.967	2.591	3.306	130.9
C12–H12...O4 ^b	0.971	2.58	3.425	144.9
C2–H2...O4	0.971	2.342	2.748	104.3
C10–H10...N1	0.967	2.413	2.803	103.6

Note. D: donor, A: acceptor. Symmetry transformation used to generate equivalent atoms.

^a2 – x, –y, –z.

^bx, –1/2 – y, –1/2 + z.

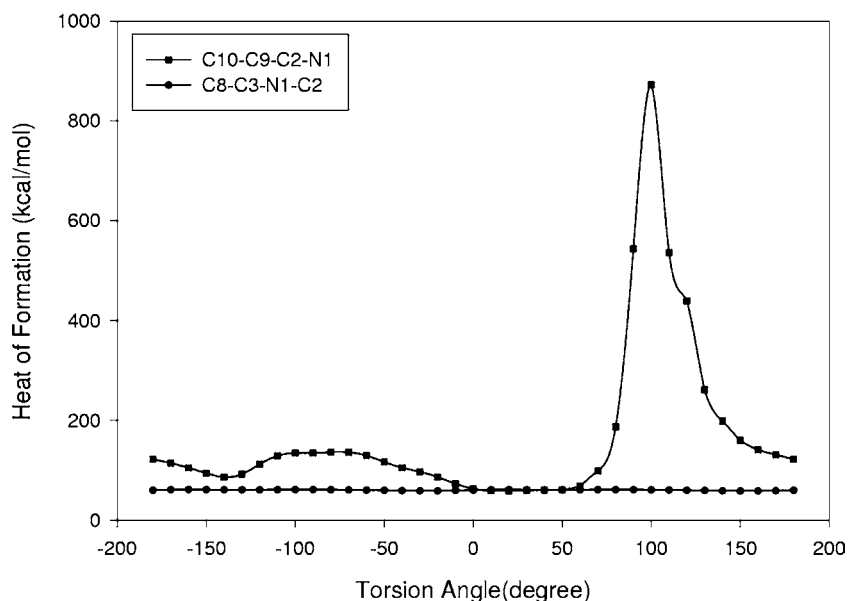


Fig. 3. Variation of heat of formation against selected two torsion angles.

comprehensively, since this method has some foibles such as partial ignorance of overlap of the atomic orbitals and the fact that the molecule is regarded as isolated (or single) molecule throughout the computations. For these reasons, some discrepancies are observed between the molecular conformations of the AM1 optimized structure (its heat of formation is 58.334 kcal/mol) and the X-ray structure. The observed conformational difference in the optimized structure is presumably due to weak inter- and intra-molecular hydrogen bonding and the contribution from packing of the molecules obeyed space group symmetry operations. The semi-empirical AM1 molecular orbital calculations were carried out in order to define the conformational flexibility of the title molecule as a function of torsion angles T1 and T2. The energy profile as function of T1 shows evident maximum in vicinity of 100°; the corresponding heat of formation value is 872.410 kcal/mol, although the energy profile as function of T2 does not show considerable changes in heat of formation. According to the conformational analysis of the title molecule, it can be stated that

torsion angle T1 supplies more contribution to the molecular energy than T2 as shown in Fig. 3.

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Supplementary material CCDC 256670 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033.

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