ELSEVIER

Journal of Molecular Structure 609 (2002) 205–212

Journal of
MOLECULAR
STRUCTURE

www.elsevier.com/locate/molstruc

Crystal structure, spectroscopic studies and conformational analyses of 5-chloro-6-nitro-2-cyclohexylmethylbenzoxazole

H. Ünver[a,*], Ö. Temiz Arpacı[b], D. Mehmet Zengin[a], T. Nuri Durlu[a,c]

[a]*Department of Physics, Faculty of Sciences, Ankara University, Tandoğan, TR-06100 Ankara, Turkey*
[b]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ankara University, Tandoğan, TR-06100 Ankara, Turkey*
[c]*Department of Physics, Faculty of Art and Sciences, University of Kırıkkale, Yahşihan, TR-71450 Kırıkkale, Turkey*

Received 1 August 2001; revised 10 December 2001; accepted 10 December 2001

Abstract

5-Chloro-6-nitro-2-cyclohexylmethylbenzoxazole (**1**) ($C_{14}H_{15}O_3N_2Cl$) has been studied by using an elemental analysis, IR, ^{1}H NMR, X-ray analysis and AM1 semi-empirical quantum mechanical methods. It crystallizes in the monoclinic space group $P2_1/c$ with $a = 8.6844(1)$, $b = 5.7169(1)$, $c = 28.8156(1)$ Å, $\beta = 92.063(1)°$, $V = 1429.70(3)$ Å^3, $Z = 4$, $D_c = 1.369$ g cm^{-3}, μ(Mo K$_\alpha$) $= 0.276$ mm^{-1} and $F(000) = 616$. The structure was solved by direct methods and refined to $R = 0.0542$ for 953 reflections [$I > 2\sigma(I)$]. The title compound is not planar. Minimum energy conformations from AM1 were calculated as a function of θ_1(O1–C7–C8–C9), θ_2(N2–C7–C8–C9), θ_3(C7–C8–C9–C10) and θ_4(C7–C8–C9–C14) varied every 5°. The optimized geometry of the crystal structure corresponding to the non-planar conformation is the most stable conformation in all calculations.

Keywords: Crystal structure; Spectroscopy; Antibacterial; Antifungal; Conformation analyses

1. Introduction

Benzoxazole derivatives constitute an important class of heterocyclic compounds for which pharmacological properties such as antibacterial and antifungal [1–4], HIV-1 reverse transcriptase inhibitor [5–10], topoisomerase inhibitor [11], antitumor [12–17] activities have been reported.

During the last twenty years, the study of the synthesis and the biological activities of benzoxazole derivatives have been investigated extensively [1–22]. To examine their chemical properties and antimicrobial activity, a series of 2,5- and/or 6-substituted benzoxazole derivatives were synthesized, one of which is the title compound. The compound (**1**) was obtained by heating cyclohexylacetic acid with 4-chloro-5-nitro-2-aminophenol in PPA (polyphosphoric acid) as the cyclodehydration reagent in a one step procedure [23]. The synthesis of the compound is shown in Fig. 1. The data obtained for (**1**) from the IR and ^{1}H NMR spectra are in agreement with the proposed structure.

2. Experimental procedures

2.1. Synthesis of 5-chloro-6-nitro-2-cyclohexylmethylbenzoxazole

A mixture of 4-chloro-5-nitro-2-aminophenol (0.01 mol) and cyclohexylacetic acid (0.015 mol)

* Corresponding author. Tel.: +90-312-212-6720.
E-mail address: unver@science.ankara.edu.tr (H. Ünver).

0022-2860/02/$ - see front matter
PII: S0022-2860(01)00975-9

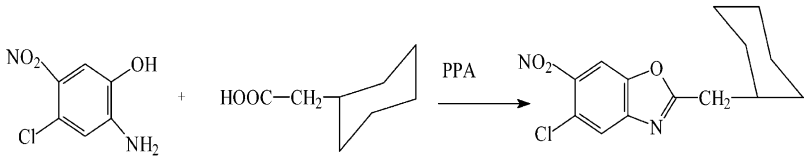

Fig. 1. Chemical structure.

was refluxed at 120–130 °C in PPA for 6 h. At the end of the reaction period, the residue was poured into ice-water and neutralized with an excess of 10% NaOH solution. The precipitate was collected, washed, dried and extracted with benzene to separate from impurities. The combined benzene extracts were dried over anhydrous sodium sulfate and evaporated in vacuo. The crude product was recrystallized by using ether and petroleum ether [23]. Yield 16%. Mp 64–66 °C. ^{1}H NMR ($CDCl_3$): 8.07 (s, 1H, H2), 7.80 (s, 1H, H5), 2.92–2.83 (d, 2H, CH_2, $^3J = 6.91$ Hz), 1.84–1.26 (m, 11H, cyclohexyl protons). IR (KBr, cm^{-1}): 3110, 2950, 1610, 1560, 1540, 1450, 1330 and 1250.

2.2. Reagents and techniques

Kieselgel HF_{254} (Merck, Darmstadt, Germany) chromatoplate (0.3 mm) was used for TLC and the solvent system was chloroform/methanol (6:0.2) for compound (**1**). The melting point was taken on a Buchi SMP 20 capillary apparatus (Buchi, Flawil, Switzerland) and is uncorrected. IR spectra were recorded by Unicam SP-1025 (Pye Unicam, Cambridge, UK) with KBr discs. ^{1}H NMR spectra were obtained with a Bruker 80 MHz spectrometer (Brucer, Billerica, USA) in d_6-chloroform and tetramethylsilane (TMS) was used as an internal standard. Elemental analyses were carried out with a Perkin Elmer model 240-C apparatus. The result of the elemental analyses (C, H, N) was within ±0.4% of the calculated amounts.

The data collection were performed on a Rigaku AFC7-S diffractometer employing graphite-monochromatized Mo K_α radiation ($\lambda = 0.71073$ Å) [24]. Data reduction and corrections for absorption and crystal decomposition (1.2%) were carried out using the TEXAN single crystal structure analysis software [25]. The structure was solved by SHELXS-97 [26] and refined with SHELXL-97 [27]. The positions of the H atoms bonded to C atoms were calculated [C–H distance 0.93 Å (H2–H5) and 0.97 Å (C8A–C8B–C10A–C10B–C11A–C11B–C12A–C12B–C13A–C13B–C14A–C14B)], and included in the structure factor calculation using a riding model. The positions of H atoms were generated from the assumed geometries, in Fourier maps and were not refined (except H8). The hydrogen atom H8 was found from difference Fourier map calculated at the end of the refinement process as a small positive electron density.

Theoretical calculations were carried out with the standard parameters using a locally modified version of the MOPAC 6.0 program package [28] which includes the AM1 Hamiltonian [29] running on a Pentium II PC starting with the optimized X-ray crystallographic coordinates [30] of (**1**). The geometry optimizations of the crystal structure of (**1**) were carried out by using the Fletcher–Powell–Davidson algorithm [31,32], which is implemented in the MOPAC 6.0 package, and the PRECISE option was used to improve the convergence criteria. To determine the conformational energy profiles, heat of formation energies were calculated as a function of the torsion angles of θ_1(O1–C7–C8–C9), θ_2(N2–C7–C8–C9), θ_3(C7–C8–C9–C10) and θ_4(C7–C8–C9–C14) from 0 to 360°, varied every 5°.

2.3. Microbiology

For both the antibacterial and antimycotic assays, the compound (**1**) was dissolved in absolute ethanol (0.8 mg ml^{-1}). Further dilutions of the compound (**1**) and standard drugs in the test medium were prepared at the required quantities of 400, 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 μg ml^{-1} concentrations with Mueller–Hinton broth and Sabouraud dextrose broth. The minimum inhibitory concentrations (MIC), were determined using the method of two-fold serial dilution technique [33,34]. In order to ensure that the solvent per se had no effect on bacterial growth, a control test was also performed containing inoculated broth supplemented with only ethanol at the same

Table 1
Crystal and experimental data

Compound	$C_{14}H_{15}N_3O_2Cl$
Color/shape	Yellow/prismatic
Formula weight	294.73
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	$a = 8.68440(1)$ Å $b = 5.71690(1)$ Å $c = 28.81560(1)$ Å $\beta = 92.063(1)°$
Volume	1429.70(3) Å^3
Z	4
Density (calculated)	1.369 g cm^{-3}
Absorption coefficient	μ(Mo K_α) = 0.276 mm^{-1}
F(000)	616
Crystal size	$0.10 \times 0.10 \times 0.20$ mm^3
θ Range for data collection	2.35–32.50°
Index ranges	$0 \le h \le 10$; $0 \le k \le 8$; $-43 \le l \le 43$
Reflections collected	3399
Independent reflections	3109 [R(int) = 0.0688]
Reflections observed ($I > 2\sigma(I)$)	953
Computer programs	SHELXS-97, SHELXL-97, ORTEP3
Refinement method	Full-matrix least-squares on F^2
Treatment of hydrogen atoms	Calculated geometrically and a riding model was used
Structure solution	Direct methods
Data/restraints/parameters	3109/0/185
Goodness-of-fit on F^2	0.953
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0542$; $wR2 = 0.1339$
R indices (all data)	$R1 = 0.2124$; $wR2 = 0.1907$
$(\Delta/\sigma)_{max}$	0.011
Largest diff. peak and hole	0.313 and −0.208 e. Å^{-3}

dilutions used in our experiments and found inactive in culture medium. Compound (**1**) was tested for their in vitro growth inhibitory activity against different bacteria and the yeast *Candida albicans RSKK 628*. Origin of bacterial strains are *Staphylococcus aureus ATCC 6538*, *Streptococcus faecalis ATCC 10541* and *Bacillus subtilis ATCC 6033* as Gram-positive and *Escherichia coli ATCC 10536*, and *Pseudomonas aeruginosa RSKK 355* as Gram-negative bacteria. RSKK strains of the microorganisms used in this study were obtained from the culture collection of Refik Saydam Health Institution of Health Ministry, Ankara and maintained at the Microbiology Department of Faculty of Pharmacy of Ankara University. Ampicillin, amoxycillin, tetracycline, streptomycin, ketoconazole and fluconazole were used as control drugs.

Table 2
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\times 10^3$ Å^2) for (**1**). U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor

Atom	x	y	z	U_{eq}[a]
Cl(1)	7139(2)	7292(3)	1183(1)	109(1)
O(1)	8044(3)	4539(5)	−720(1)	73(1)
O(2)	4820(4)	1391(8)	561(1)	120(2)
O(3)	5939(7)	2795(8)	1163(2)	172(2)
N(1)	5702(6)	2694(9)	742(2)	95(1)
N(2)	9239(4)	7820(6)	−467(1)	68(1)
C(1)	7711(4)	4814(7)	−260(1)	62(1)
C(2)	6822(4)	3436(7)	8(2)	68(1)
C(3)	6683(5)	4198(8)	459(2)	69(1)
C(4)	7389(5)	6228(8)	629(1)	68(1)
C(5)	8288(5)	7558(7)	349(1)	67(1)
C(6)	8452(4)	6815(7)	−104(1)	60(1)
C(7)	8960(5)	6442(9)	−814(2)	69(1)
C(8)	9471(5)	6636(9)	−1294(1)	82(1)
C(9)	8208(5)	7371(8)	−1648(1)	65(1)
C(10)	7644(5)	9829(8)	−1573(1)	79(1)
C(11)	6418(5)	10,534(9)	−1937(2)	99(2)
C(12)	6997(6)	10,213(13)	−2426(2)	121(2)
C(13)	7570(6)	7781(12)	−2502(2)	119(2)
C(14)	8779(5)	7098(9)	−2136(1)	91(2)
H(9)	7350(4)	6370(7)	−1628(12)	78

[a] $U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$.

2.4. Antibacterial and antifungal assay

The cultures were obtained from Mueller–Hinton broth (Difco) for all the bacterial strains after 24 h of incubation at 37 ± 1 °C. The yeast *C. albicans* was maintained in Sabouraud dextrose broth (Difco) after incubation for 24 h at 25 ± 1 °C. Testing was carried out in Mueller–Hinton broth and Sabouraud dextrose broth (Difco) at pH 7.4 and the two-fold serial dilution technique was applied. The final inoculum size was 10^5 CFU ml^{-1} for the antibacterial assay and 10^4 CFU ml^{-1} for the antifungal assay. A set of tubes containing only inoculated broth was kept as controls. For the antibacterial assay after incubation for 24 h at 37 ± 1 °C and after incubation for 48 h at 25 ± 1 °C for the antifungal assay, the last tube with no growth of microorganism and/or yeast was recorded to represent the MIC expressed in μg ml^{-1}. Every experiment in the antibacterial and antifungal assays was replicated twice in order to define the MIC values.

Table 3
Bond distances (Å) and bond angles (°) with e.s.d.s in parentheses, respectively

Cl(1)–C(4)	1.728(4)	O(1)–C(1)	1.375(4)
O(1)–C(7)	1.380(5)	O(2)–N(1)	1.177(5)
O(3)–N(1)	1.227(5)	N(1)–C(3)	1.475(6)
N(2)–C(7)	1.288(5)	N(2)–C(6)	1.396(5)
C(1)–C(2)	1.362(5)	C(1)–C(6)	1.380(5)
C(2)–C(3)	1.382(6)	C(3)–C(4)	1.393(6)
C(4)–C(5)	1.373(5)	C(5)–C(6)	1.384(5)
C(7)–C(8)	1.472(5)	C(8)–C(9)	1.529(5)
C(9)–C(10)	1.506(5)	C(9)–C(14)	1.515(5)
C(10)–C(11)	1.521(6)	C(11)–C(12)	1.526(6)
C(12)–C(13)	1.496(7)	C(13)–C(14)	1.514(6)
C(9)–H(9)	0.940(4)		
C(1)–O(1)–C(7)	104.0(3)	O(2)–N(1)–O(3)	123.5(5)
O(2)–N(1)–C(3)	120.3(5)	O(3)–N(1)–C(3)	116.0(5)
C(7)–N(2)–C(6)	104.3(3)	C(2)–C(1)–O(1)	128.5(4)
C(2)–C(1)–C(6)	124.2(4)	O(1)–C(1)–C(6)	107.3(3)
C(1)–C(2)–C(3)	114.9(4)	C(2)–C(3)–C(4)	122.8(4)
C(2)–C(3)–N(1)	114.0(5)	C(4)–C(3)–N(1)	123.2(4)
C(5)–C(4)–C(3)	120.5(4)	C(5)–C(4)–Cl(1)	116.1(4)
C(3)–C(4)–Cl(1)	123.3(4)	C(4)–C(5)–C(6)	117.6(4)
C(1)–C(6)–C(5)	120.0(4)	C(1)–C(6)–N(2)	109.3(3)
C(5)–C(6)–N(2)	130.7(4)	N(2)–C(7)–O(1)	115.1(3)
N(2)–C(7)–C(8)	128.9(4)	O(1)–C(7)–C(8)	116.0(4)
C(7)–C(8)–C(9)	114.5(3)	C(10)–C(9)–C(14)	110.4(4)
C(10)–C(9)–C(8)	112.9(4)	C(14)–C(9)–C(8)	109.9(3)
C(9)–C(10)–C(11)	111.8(4)	C(10)–C(11)–C(12)	111.1(4)
C(13)–C(12)–C(11)	111.7(4)	C(12)–C(13)–C(14)	111.3(5)
C(13)–C(14)–(C9)	112.3(4)		

3. Results and discussion

3.1. Spectroscopic studies

The observed vibrational bands in the 1250–3110 cm^{-1} in the compound studied are given in experimental part. Absorption bands at 1610 ($\nu_{C=N}$), 3110 (ν_{C-H}, Ar–H), 1560 ($\nu_{C=C}$), 2950, 1540, 1450, 1330 and 1250 cm^{-1} were observed.

The NMR data for (**1**) were as follows: $\delta =$ 8.07 ppm s, 1H (H2), $\delta = 7.80$ ppm s, 1H (H5), $\delta =$ 2.92–2.83 ppm d, 2H (H8A, H8B) ($^3J = 6.91$ Hz), $\delta = 1.84$–1.26 ppm m, (11H) cyclohexyl protons.

3.2. Microbiological studies

The compound (**1**) showed antibacterial activity against the Gram-positive and Gram-negative bacteria

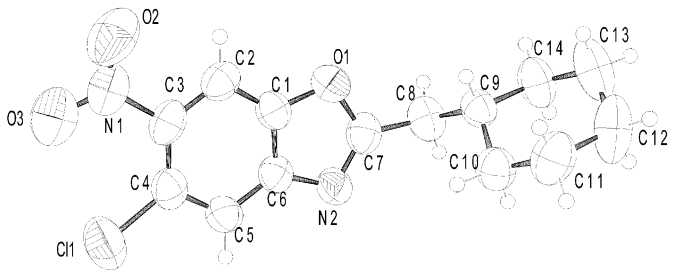

Fig. 2. The molecular structure of the title compound (**1**). Displacement ellipsoids are plotted at the 50% probability level [28].

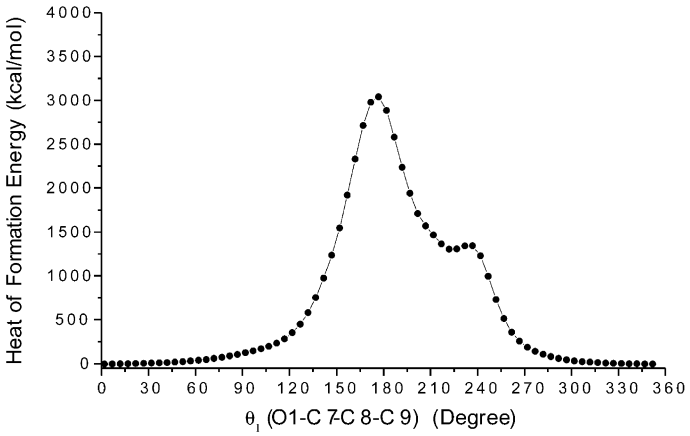

Fig. 3. AM1 calculated conformation energy of the θ_1(O1–C7–C8–C9) torsion angle.

with a MIC value of 50 μg ml^{-1}. The compound (**1**) were also tested against *C. albicans* for their antimycotic activity and indicated significant antimycotic activity performing MIC value 25 μg ml^{-1}.

3.3. Crystal structure and semi-empirical studies

The details of the X-ray data collection, structure solution and structure refinements were given in Table 1. The final fractional atomic coordinates and thermal parameters were given in Table 2. Bond distances and angles are listed in Table 3 and an ORTEP view of the molecular structure is given in Figs. 1 and 2 [35].

The title molecule is not planar. The compound (**1**) moieties **A** [O1, C1, C2, C3, N1, O2, O3, C4, Cl1, C5, C6, N2, planar with a maximum deviation of 0.4110(0.0047) Å for the O3 atom] and **B** [C7, C8, C9, C10, C11, C12, C13, C14, planar with a maximum deviation of −0.2965(0.0043) Å for the C13 atom] are inclined at an angle of 76.0(1)° reflecting mainly the twist about C7–C8 [N2–C7–C8–C9, −106.3(1)°].

The bond lengths and angles for the benzimidazole moiety of the molecule are in good agreement, within experimental errors, with those observed in other benzimidazole derivatives [36,37]. The N2–C6 and N2–C7 bond distances were found to be 1.396(5) and 1.288(5) Å, respectively. The corresponding

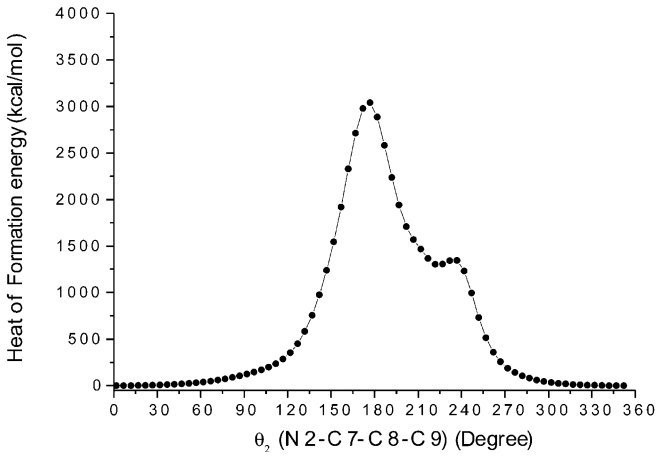

Fig. 4. AM1 calculated conformation energy of the θ_2(N2–C7–C8–C9) torsion angle.

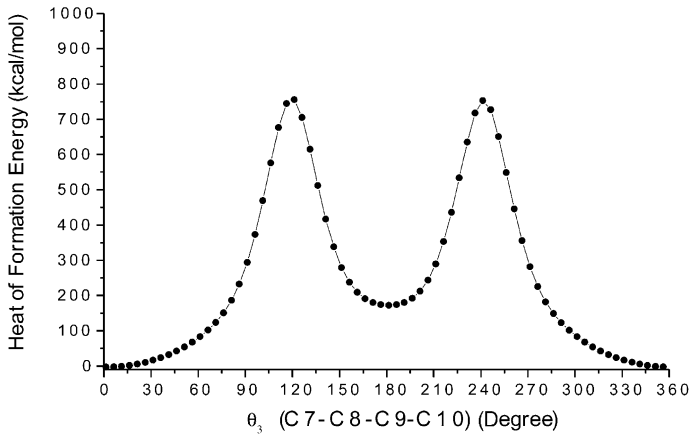

Fig. 5. AM1 calculated conformation energy of the θ_3(C7–C8–C9–C10) torsion angle.

values in 2,5-dichloro-1-(*p*-chlorobenzyl)-1*H*-benzimidazole [36] 1.391(2) and 1.296(2) Å and 1-(*p*-fluorophenylmethyl)-2-(4-methyl-1-piperazinyl)-1*H*-benzimidazole hydrogen fumarate [37] are 1.395(5) and 1.319(5) Å.

In order to define the conformational flexibility of the title molecule (**1**), semi-empirical calculations using the AM1 molecular orbital method were carried out. The AM1 optimized geometry and conformations of the title compound are in agreement with those crystallographically observed. The molecular energy can be divided into bonded and non-bonded contributions. The bonded energy is considered to be independent of torsion angle changes and therefore vanishes when relative conformer energies are calculated as in our calculations. The non-bonded energy (E_N) is then further separated into torsional (E_T), steric (E_S) and electrostatic (E_{ES}) contributions

$$E_N = E_T + E_S + E_{ES} \quad (1)$$

where the torsional energy (E_T) is that parts of the total energy which does not arrive from the steric or electrostatic form.

The theoretical calculations were performed on the torsion angles of θ_1(O1–C7–C8–C9) (Fig. 3), θ_2(N2–C7–C8–C9) (Fig. 4), θ_3(C7–C8–C9–C10) (Fig. 5), θ_4(C7–C8–C9–C14) (Fig. 6) and specially calculated energy results were given in Table 4.

The energy profile of θ_1(O1–C7–C8–C9) shows two maxima at 177 and 236°. The largest energy

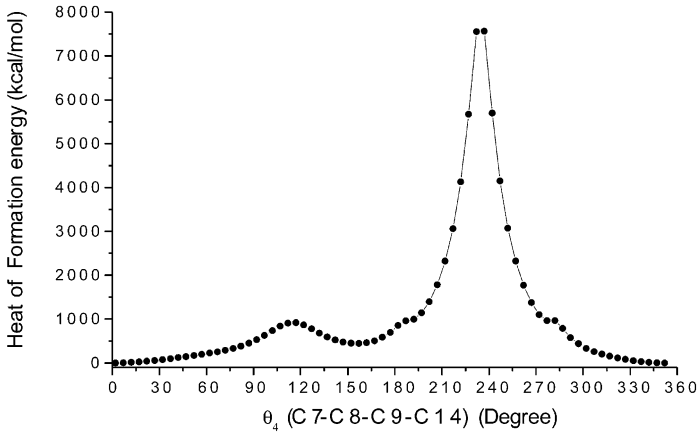

Fig. 6. AM1 calculated conformation energy of the θ_4(C7–C8–C9–C14) torsion angle.

Table 4
The calculated energies of selected torsion angles

	θ_1 (max.) (°)	E_1 (kcal mol^{-1})	θ_2 (max.) (°)	E_2 (kcal mol^{-1})
θ_1(O1–C7–C8–C9)	177	3040	236	1344
θ_2(N2–C7–C8–C9)	176	3041	237	1345
θ_3(C7–C8–C9–C10)	121	755	242	753
θ_4(C7–C8–C9–C14)	117	920	237	7563

barrier is due to steric interactions between H9 and H10A–H10B. The smallest energy barrier arises from the steric interaction of the H9–H10A. The energy profile of θ_1(O1–C7–C8–C9) also shows two maxima at 176 and 237°. The largest energy barrier is due to steric interactions between H9 and H10A–H10B. The smallest energy barrier arises from the steric interaction of the H9–H10A. The θ_1(O1–C7–C8–C9) and θ_2(N2–C7–C8–C9) torsion angles control the planarity of (**1**). The non-planar conformation of the title compound corresponding to zero values of the θ_1(O1–C7–C8–C9) and θ_2(N2–C7–C8–C9) torsion angles is the most stable conformation (Figs. 3 and 4). The energy profile of θ_3(C7–C8–C9–C10) shows two maxima at 121 and 242°. The energy barrier for two maxima is due to steric interactions between H9 and H14A (Fig. 5). In the energy profile as function of θ_4(C7–C8–C9–C14) torsion angle, there are two steric interactions maxima at 117 and 237°, one of them is very strong between H8A and H9 and another weak steric interaction of the H9–H10A (Fig. 6).

In summary, the AM1 optimized geometry of the crystal structure of the investigated compound corresponding to non-planar conformation is the most stable conformation in all considered calculations. The results strongly indicate that the most stable conformation is primarily determined by non-bonded hydrogen–hydrogen repulsions.

References

[1] T. Hisano, M. Ichikawa, K. Tsumoto, M. Tasaki, Chem. Pharm. Bull. 30 (1982) 2996.
[2] M. Prudhomme, J. Guyot, G. Jeminet, J. Antibiot. 39 (1986) 934.
[3] S. Ersan, S. Nacak, R. Berkem, T. Özden, Arzneim.-Forsch. 47 (1997) 963.
[4] H.M. El-Shaaer, S.A. Abdel-Aziz, H.A. Allimony, R.M. Abdel-Rahman, Pharmazie 52 (1997) 585.
[5] W.S. Saari, J.S. Wai, T.E. Fisher, C.M. Thomas, J.M. Hoffman, C.S. Roomey, A.M. Smith, J.H. Jones, D.L. Bamberger, M.E. Goldman, J.A. O'brien, J.H. Nunberg, J.C. Quintero, Q.A. Schleif, E.A. Emini, P.S. Anderson, J. Med. Chem. 35 (1992) 3792.
[6] M.E. Goldman, J.A. O'brien, T.L. Ruffing, W.A. Schleif, V.V. Sardana, V.W. Byrnes, J.H. Condra, J.M. Hoffman, E.A. Emini, Antimicrob. Agents Chemother. 37 (1993) 947.
[7] J.M. Hoffman, A.M. Smith, C.S. Rooney, T.E. Fisher, J.S. Wai, C.M. Thomas, D.L. Bambmerger, J.L. Barnes, T.M. Williams, J.H. Jones, B.D. Olson, J.A. O'brien, M.E. Goldmah, J.H. Nunberg, J.C. Quintero, W.A. Schleif, E.A. Emini, P.S. Anderson, J. Med. Chem. 36 (1993) 953.
[8] R.T. Davey, R.L. Dewar, G.F. Reed, M.B. Vasudevachari, M.A. Polis, J.A. Kovacs, J. Falloon, R.E. Walker, H. Masur, S.E. Haneiwich, D.G. O'neil, M.R. Decker, J.A. Metcalf, M.A. Deloria, O.L. Laskin, N. Salzman, H.C. Lone, Proc. Natl Acad. Sci. 90 (1993) 5608.
[9] S. Staszewski, F.E. Massari, A. Kober, R. Göhler, S. Durr, K.W. Anderson, C.L. Schneider, J.A. Waterburry, K.K. Bakshi, V.I. Taylor, J. Infect Dis. 171 (1995) 1159.
[10] D.B. Olsen, S.S. Carroll, J.C. Culberson, J.A. Shafer, L.C. Kuo, Nucl. Acid Res. 22 (1994) 1437.
[11] J.S. Kim, Q. Sun, B. Gatto, C. Yu, A. Liu, L.F. Liu, E.J. La Voie, Bioorg. Med. Chem. 4 (1996) 621.
[12] M. Ueki, K. Ueno, S. Miyadoh, K. Abe, K. Shibata, M. Taniguchi, J. Antibiot. 46 (1993) 1089.
[13] D.F. Shi, T.D. Bradshaw, S. Wrigley, C.J. McCall, P. Lelieveld, I. Fichtner, M.F.G. Stevens, J. Med. Chem. 39 (1996) 3375.
[14] M. DeLuca, S. Kerwin, Tetrahedron Lett. 38 (1997) 199.
[15] M.B. Reynolds, M. DeLuca, S. Kerwin, Bioorg. Chem. 27 (1999) 326.
[16] Z.M. Nofal, M. El-Zahar, S.S. Abd El-Karim, Molecules 5 (2000) 99.
[17] S. Sato, T. Kajiura, M. Noguchi, K. Takehana, T. Kobayashi, T. Tsuji, J. Antibiot. 54 (2001) 102.
[18] E. Şener, İ. Yalçın, E. Sungur, Quant. Struct. Act. Relat. 10 (1991) 223.
[19] E. Şener, İ. Yalçın, Ö. Temiz, İ. Ören, A. Akın, N. Uçartürk, Farmacology 52 (1996) 99.
[20] İ. Ören, Ö. Temiz, İ. Yalçın, E. Şener, A. Akın, N. Uçartürk, Arzneim.-Forsch. 47 (1997) 1393.
[21] Ö. Temiz, İ. Ören, E. Şener, İ. Yalçın, N. Uçartürk, Farmacology 53 (1998) 337.
[22] İ. Yalçın, İ. Ören, E. Şener, A. Akın, N. Uçartürk, Eur. J. Med. Chem. 27 (1992) 401.

[23] İ. Ören, Ö. Temiz, İ. Yalçın, E. Şener, N. Altanlar, Eur. J. Pharm. Sci. (1998) 153.
[24] Molecular Structure Corporation, MSC/AFC Diffractometer Control Software, MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA, 1994.
[25] Molecular Structure Corporation, TEXAN for Windows Version 1.03, Single Crystal Structure Analysis Software, Version 1.03, MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA, 1997.
[26] G.M. Sheldrick, Acta Crystallogr. A46 (1990) 467.
[27] G.M. Sheldrick, SHELXL-97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1997.
[28] J.P. Stewart, MOPAC Version 6.0, Quantum Chemistry Program Exchange 581, Indiana University, USA, 1989.
[29] M.J.S. Dewar, E.G. Zeobisch, E.F. Healy, J.J.P. Stewart, J. Am. Chem. Soc. 197 (1985) 3902.
[30] F.H. Allen, O. Kennard, D.G. Watson, L. Brammer, A.G. Orpen, J. Chem. Soc., Perkin Trans. 1 11 (1987).
[31] R. Fletcher, M.J.D. Powell, Comput. J. 6 (1963) 163.
[32] W.C. Davidson, Comput. J. 10 (1968) 406.
[33] E.S. Charles, V.K. Agrawal, S. Sharma, R.N. Iyer, Eur. J. Med. Chem., Chim. Ther. 14 (1979) 435.
[34] S. Shadomy, A. Espinel, Manual of Clinical Microbiology, American Society of Microbiology, Washington, DC, 1980 p. 647.
[35] L.J. Farrugia, J. Appl. Crystallogr. 30 (1997) 565.
[36] E. Kendi, S. Özbey, H. Göker, Acta Crystallogr. C55 (1999) 243.
[37] S. Özbey, E. Kendi, H. Göker, M. Tunçbilek, J. Chem. Crystallogr. 28 (1998) 461.