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Spectral and Theoretical studies of some *N*-nitroso-*t*(3)-isopropyl-r(2),*c*(6)-bis(*p*-halophenyl)piperidin-4-ones

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Abstract

N-nitroso-*t*(3)-isopropyl-r(2),*c*(6)-bis(*p*-halorophenyl)piperidin-4-ones **1–2** and their parent piperidin-4-ones **3-4** were synthesized and Characterized by IR, Mass , ^{1}H and ^{13}C NMR spectral studies. The spectra reveal the presence of two rotameric forms (*syn* and *anti*) in solution for **1–2**. ^{1}H-^{1}H and ^{1}H-^{13}C COSY spectra have been recorded to assist the assignment of the signals for the *syn* and *anti* isomers of **1–2**. Coupling constants predict an equilibrium mixture of boat conformation **B1**/**B5** and alternate chair form **CA** for **1–2**. The molecular structures of **1–2** were also determined using DFT calculations available in Dmol^{3} package and the results have been compared with the results derived from spectral studies and single crystal measurements. The effect of varying the substituents at nitrogen on the ^{1}H and ^{13}C chemical shifts has been analyzed in detail.

Keywords: *N*-nitrosopiperidin-4-ones, Spectral, Theoretical, Conformation, Dmol^{3} package

Contents

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1. Introduction

Heterocyclic system which contain nitrogen as heteroatom, cause attention to chemists and drug designers till now. In this connection, imidazolidines which contain two nitrogen atoms, dioxolanes which contains two oxygen atoms and piperidine which contains one nitrogen atom are important. Nitrogen containing aliphatic heterocyclic compounds were reported to possess a lot of pharmacological activity[1], such as pyrrolidinyl derivatives, etc. Particularly many piperidine derivatives were reported to possess pharmacological activity and form an essential part of the molecular structure of important drugs[2,3], Thioridizine (Antipshycotics) and Haloperidol. Esters of 4–phenyl-4-piperidinol also have analgesic properties[4]. Piperidones were also reported to possess anti-inflammatory, Central nervous system, local anesthetics and anti microbial activity[5]. Oximes of piperidine-4-ones were reported to have antifungal activity against niger and N-nitroso-r-2, c-6-diaryl-3-methyl-piperidin-4-one oximes were reported to possess anticancer activity[6]. Most of the piperidine precursors are known to exist in chair conformation. Electron withdrawing groups (–NO, –CHO, –COR and –CONHPh) introduced at the nitrogen atom profoundly affect the

conformations of the heterocyclic ring and orientation of the substituents in 2,6-dialkyl- and 2,6-diaryl substituted piperidines[7–17] since severe $A^{1,3}$ strain exists in the normal chair conformation. In all these cases conformations which avoid $A^{1,3}$ strain are favored. In an effort to create new derivatives of pharmacologically active piperidones existing in other than normal chair conformation, the present investigation was undertaken. Two *N*-nitroso-r(2),*c*(6)-bis(*p*-halophenyl)-*t*(3)-isopropylpiperidin-4-ones **1–2** were synthesized in the present study and their conformational behavior was analyzed using ^{1}H and ^{13}C NMR spectroscopy. The preferred conformations were further confirmed by means of conformational analysis performed by Dmol^3 calculations.

2. Materials and Methods

2.1 Preparation of compounds

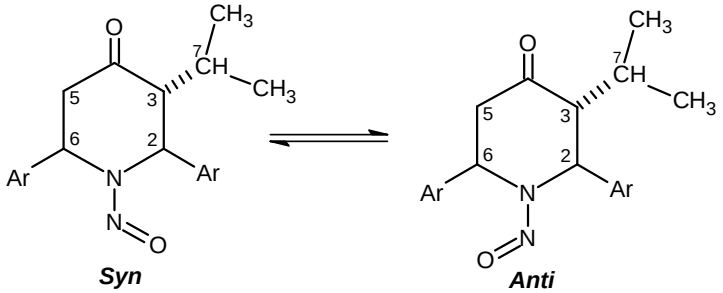
The compound *t*(3)-isopropyl-r(2),*c*(6)-bis(*p*-chlorophenyl)piperidin-4-one **3-4** was prepared according to the procedure described in literature[18] It was recrystallized twice from benzene-petroleum ether mixture. Yield: 75%; m.p: 114°C(**3**) , 80%; m.p: 83°C (**4**). The *N*-nitroso derivative **1** was prepared from **3** as per procedure mentioned in the literature [19] and the product was purified by column chromatography using benzene:ethyl acetate (8:2) as a eluent. The yield was 70%. The compound melted at 98°C. IR (cm^{-1}): 3407.25, 2962.80, 1715.35, 1597.97, 1493.38, 1455.91, 1351.96, 1310.80, 1223.92, 1149.78, 1093.04, 1010.89, 905.44, 824.98 and 772.74. The *N*-nitroso derivative **2** was prepared from **4** as per procedure mentioned in the literature [19] and the product was purified by column chromatography using benzene:ethyl acetate (8:2) as a eluent. The yield was 70%. The compound melted at 104°C. IR (cm^{-1}): 3415.45, 2968.70, 1725.65, 1599.57, 1498.78, 1465.71, 1357.93, 1320.60, 1243.72, 1153.63, 1098.73, 1015.98, 917.62, 837.76 and 783.46.

2.2 Recording of spectra

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 NMR spectrometer operating at 400 and 100.6 MHz for ^{1}H and ^{13}C respectively. The ^{1}H-^{1}H and ^{1}H-^{13}C COSY spectra were recorded on a Bruker DRX 500 NMR spectrometer using standard parameters. Solutions were prepared by dissolving 10 mg (^{1}H) and 50 mg (^{13}C) of the compound in 0.5 mL of solvent ($CDCl_3$). All NMR measurements were made in 5 mm NMR tubes.

3. Results and Discussion

The high resolution ^{1}H and ^{13}C NMR spectra of *N*-nitroso-*t*(3)-isopropyl-r(2),*c*(6)-bis (*p*-chlorophenyl) -piperidin-4-one(**1**), *N*-nitroso-*t*(3)-isopropyl-r(2),*c*(6)-bis(*p*-flurophenyl)-peridin-4-one (**2**) and their parent compound *t*(3)-isopropyl-r(2),*c*(6)-bis(*p*-chlorophenyl)piperidin-4-one(**3**), *t*(3)-isopropyl-r(2),*c*(6)-bis(*p*-flurophenyl)piperidin-4-one (**4**) have been recorded in $CDCl_3$ and analyzed. The structures of the synthesized compounds **1–4** are indicated in figure 1. The ^{1}H NMR spectra of *N*-nitroso-*t*(3)-isopropyl derivatives **1-2** contained two distinct signals for each α protons at room temperature. The observation of two sets of signals in **1–2** suggests the presence of restricted rotation around N–N bonds and establishment of equilibrium between two rotamers with coplanar orientation of *N*-nitroso group in these derivatives. The two rotamers are labeled as *syn* [nitroso oxygen is *syn* to isopropyl group at C(3)] and *anti* [nitroso oxygen is *anti* to isopropyl group at C(3)] isomers (figure 2). Based on intensities and integrals, the signals for one rotamer can be easily differentiated from the other rotamer. For all the compounds ^{1}H-^{1}H and ^{1}H-^{13}C COSY spectra were recorded to confirm the assignment of signals. In the present study the chemical shift of H(6) proton can be taken as a criterion to assign the signals for *syn* and *anti* isomers.



Ar = p-chlorophenyl, p-flurophenyl

Figure. 2

Figure 2. *Syn* and *anti* rotamers of 1–2

The chemical shift of H(2) proton is influenced by the magnetic anisotropic effect of nearby isopropyl group which in turn depends on the conformation of isopropyl group. The conformation of *N*-nitroso derivatives is expected to be different from normal chair conformation since in normal chair conformation severe allylic strain exists. Therefore, H(6) chemical shifts are used to differentiate between *syn* and *anti* isomers. It has been previously established that *syn*

α protons (*syn* with respect to carbonyl oxygen) are deshielded to a greater extent than the *anti* α protons (*anti* with respect to carbonyl oxygen) due to *N*-acylation [7,17] .In the parent *t*(3)-isopropylpiperidin-4-ones **3-4** H(2) resonates at upfield (lower frequency) relative to H(6) due to magnetic anisotropic effect of nearby equatorial isopropyl group at C(3). Therefore, among the two sets of signals in the *N*-acyl derivatives, the set in which H(6) is considerably lower can be assigned to the *syn* isomer [H(6) *syn* < H(6) *anti*]. Literature [8a,9,19] reveals that *syn* α protons should resonate however at lower frequency than *anti* α protons due to *N*-nitrosation. Among the two sets of signals in the *N*-nitroso derivatives **1-2** the set in which H(6) is considerably lower can be assigned to the *anti* isomer [(H(6) *anti* < H(6) *syn*].The chemical shifts and the coupling constants [^{1}H and ^{13}C] of **1–4** are given in tables 1–3.

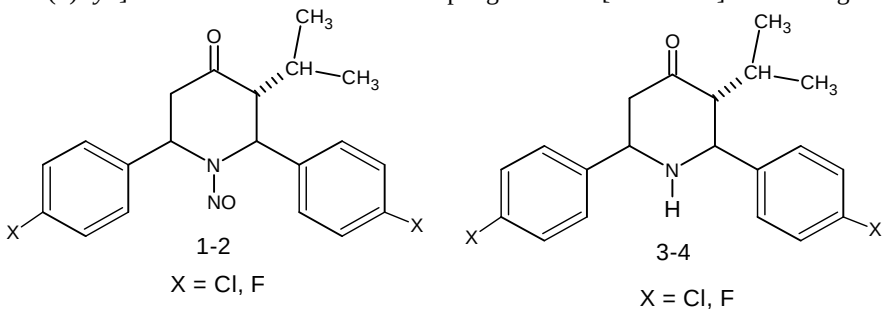


Figure. 1

Figure 1. Structures of synthesized compounds 1–4.

Table 1. ^{1}H Chemical shifts (ppm) of *N*-nitroso-*t*(3)-isopropylpiperidin-4-one derivatives 1–2 and their Parent compounds 3-4

Comp.		H(2)	H(3)	H_{5e}	H_{5a}	H(6)	Alkyl protons		Other protons
							CH	CH_3	
1	*syn* (major)	6.76 (s)	2.73 (dd)	3.15–3.12		6.43 (dd)	1.75 (m)	1.06 (d) 0.94 (d)	6.70 (d), 6.72 (d), 6.94 (d), 6.95 (d),
	anti (minor)	6.49 (s)	2.95 (dd)	2.80–2.78		6.23 (t)	1.92 (m)	1.15 (d) 1.02 (d)	6.99 (d), 7.02 (d) 7.05 (d), 7.14 (d), 7.15 (d), 7.17 (d)
2	*syn* (minor)	6.72 (s)	2.68 (dd)	3.10–3.12		6.40 (dd)	1.70 (m)	1.05 (d) 0.92 (d)	6.68(d), 6.70(d), 6.91 (d), 6.93 (d),
	anti (major)	6.45 (s)	2.85(dd)	2.80–2.76		6.21 (t)	1.90 (m)	1.13 (d) 1.02 (d)	6.97 (d), 7.00 (d) 7.02(d), 7.11 (d), 7.13 (d), 7.15 (d)
3		3.98 (d)	2.63–2.52			4.08 (dd)	1.65 (m)	1.03 (d) 0.89 (d)	7.37–7.28, 7.44 (d)
4		3.98 (d)	2.65–2.58	2.53	2.65–2.58	4.07 (dd)	1.66 (m)	1.01 (d) 0.86 (d)	7.05–7.02, 7.43 (d)

Table 2. ^{13}C Chemical shifts (ppm) of *N*-nitroso-*t*(3)-isopropylpiperidin-4-one derivatives 1–2 and their Parent compounds 3-4

Comp.		C(2)	C(3)	C(4)	C(5)	C(6)	Alkyl carbons		Other carbons
							CH	CH_3	
1	*syn* (major)	51.61	58.75	208.05	41.28	60.75	29.01	21.48 19.88	128.19, 128.35, 128.76, 128.87,
	anti (minor)	62.44	58.38	207.57	41.28	51.61	28.58	20.64 20.09	134.29, 134.53, 136.03, 136.20
2	*syn* (minor)	51.60	58.73	208.20	41.25	60.72	29.00	21.45 19.86	128.17, 128.33, 128.75, 128.84,
	anti (major)	62.42	58.35	207.83	41.23	51.60	28.56	20.64 20.09	134.27, 134.51, 136.00, 136.20
3		63.84	60.39	207.85	50.09	61.04	26.01	20.90 17.64	127.81, 128.80, 128.87, 129.14
4		63.83	60.40	208.15	51.91	61.20	25.88	20.78 17.68	115.50, 128.10, 129.37

3.1. Ring conformations

The observation of one large and one small coupling about C(5)–C(6) bond and large coupling about C(2)–C(3) bond in the parent piperidin-4-ones **3-4** reveals that this compound adopts normal chair conformation with the equatorial orientations of *p*-halophenyl rings at C(2) and C(6) and isopropyl group at C(3). For **3** single crystal measurements were also made [20]. The single crystal measurements reveal normal chair conformation with equatorial orientations of all substituents. The molecule belongs to the monoclinic crystal lattice ($P2_1/c$). The ORTEP structure is given in figure 3.

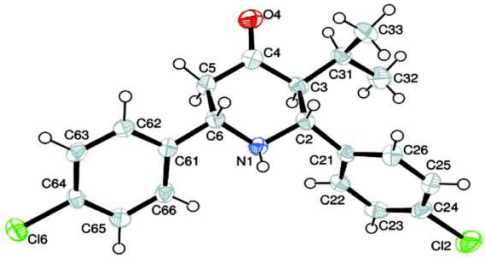
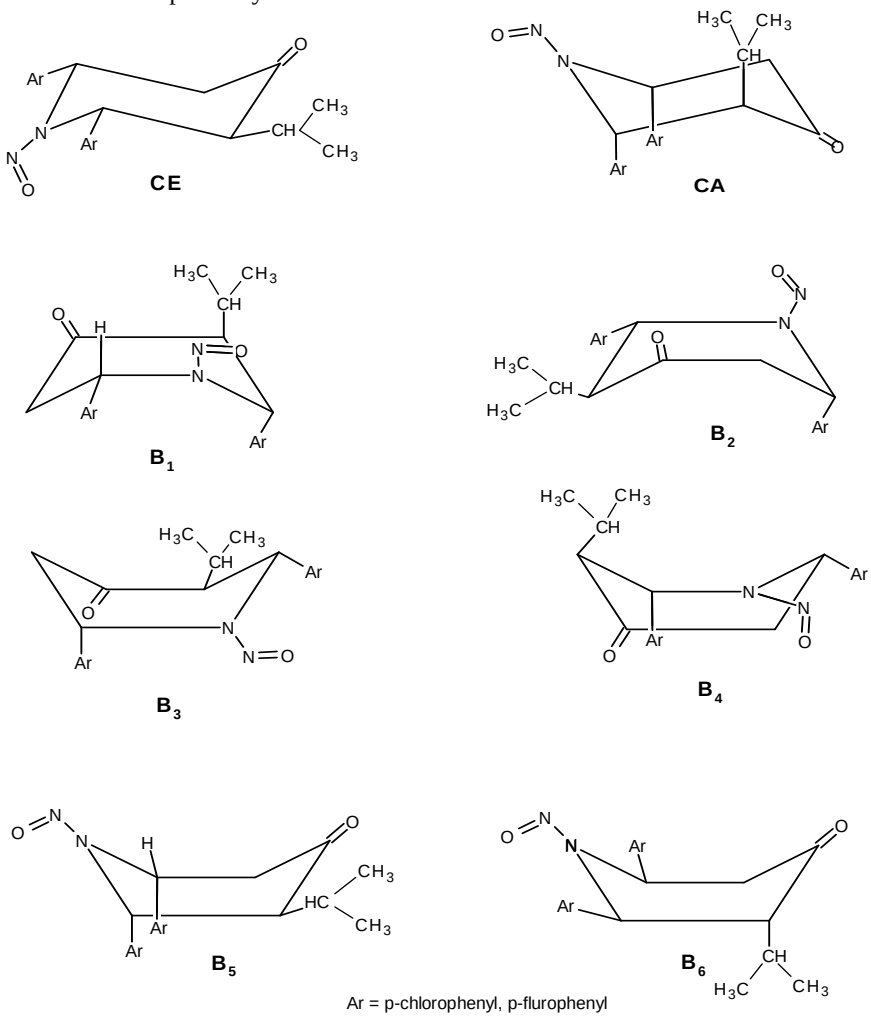


Figure 3

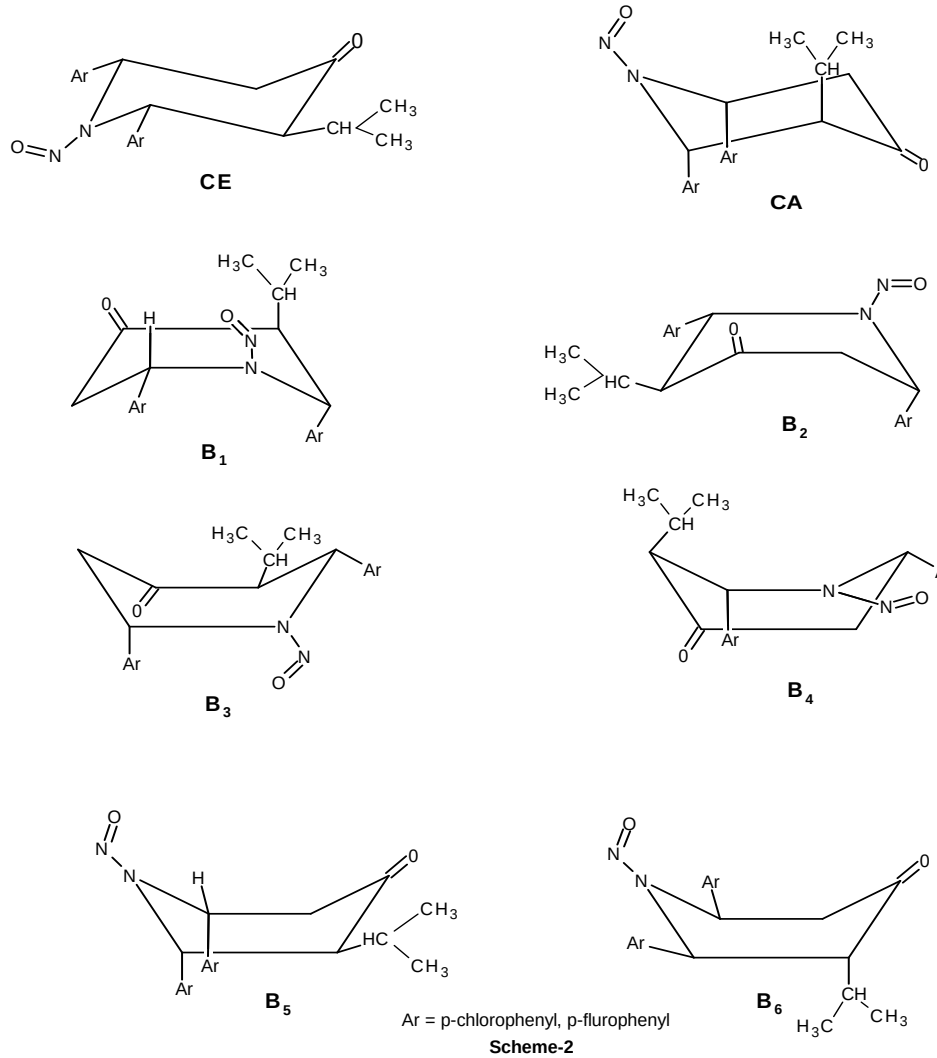
Figure 3. ORTEP structure of 3

The coupling constants about C(2)–C(3) bond in both the *syn* and *anti* isomers of *N*-nitroso derivatives **1-2** are found to be very small (<1 Hz) [singlet for H(2)]. The observation of total width of 13.47 Hz about C(5)–C(6) bond in the *anti* isomer and one large (7.14 Hz) and one small coupling (3.61 Hz) in the *syn* isomer is in contrast to the values observed in the parent piperidin-4-ones **3-4**. These observations cannot be accounted by normal chair conformation **CE** with equatorial orientations of all the substituents. The possible conformations for the *syn* and *anti* isomers of **1-2** are shown in schemes 1 and 2 respectively.



Scheme-1

Scheme 1. Possible conformations for the *syn* isomer of 1-2



Scheme 2. Possible conformations for the *anti* isomer of 1-2.

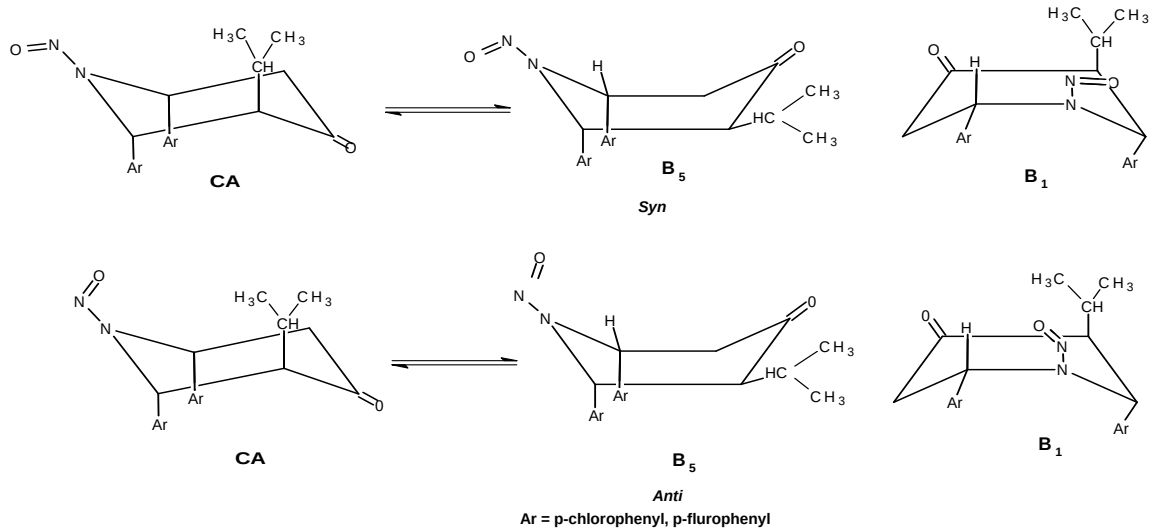


Figure 4. Favored conformations of 1–2

In the *syn* form of **1-2** the normal chair conformation **CE**, boat forms **B3** and **B6** shown in Scheme 1 are ruled out based on $A^{1,3}$ strain and the boat conformations **B2** and **B3** are ruled out based on the singlet for H(2). The possible conformations are reduced to **CA**, **B1** and **B5**. The observed two couplings about C(5)–C(6) bond (7.14, 3.60 Hz) and singlet for H(2) suggest that the major conformer is highly distorted alternate chair form **CA** only. A small amount of boat form **B5**/**B1** may also be present in solution in addition to the alternate chair form **CA**. Thus, the *syn* isomer of **1-2** exists as an equilibrium mixture of alternate chair form **CA** (major) and boat form **B5** (minor) or **B1** (minor).

The conformations **CE**, **B4**, **B6**, **B2** and **B3** shown in Scheme 2 for the *anti* isomer are ruled out based on $A^{1,3}$ strain and the singlet observed for H(2). The observation of total width of 13.47 Hz about C(5)–C(6) bond suggests that *N*-nitroso derivatives **1-2** cannot exist in single conformation. It can exist as an equilibrium mixture of two or three conformers. An equilibrium mixture of alternate chair form **CA** and boat form **B5**/**B1** can account the observed couplings about C(5)–C(6) bond and singlet for H(2) in the *anti* isomer of **1-2** also. The favored conformations predicted from coupling constant analysis of the *N*-nitroso derivatives **1–2** are given in Figure 4.

For **1** single crystal measurements were also made [21]. The molecule belongs to the triclinic crystal lattice. The ORTEP and close packed crystal structures are given in figures 5 and 6 respectively.

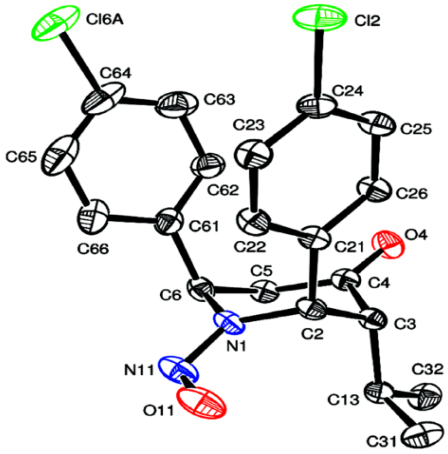


Figure 5

Figure 5. ORTEP structure of 1.

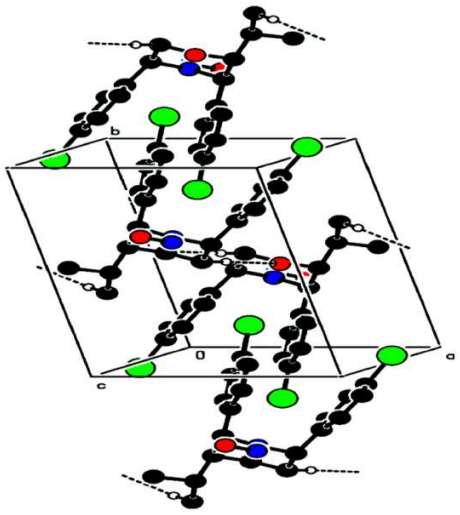


Figure 6

Figure 6. Close packed structure of 1.

The crystal data are given below:

Crystal data	
$C_{20}H_{20}Cl_2N_2O_2$	$\gamma = 104.549(3)°$
$M_r = 391.28$	$V = 953.95(6)$ Å^3
Triclinic, *P*1	$Z = 2$
$a = 8.2771(2)$ Å	CuKα radiation
$b = 11.1921(4)$Å	$\mu = 3.20$ mm^{-1}
$c = 11.2351(4)$Å	$T = 200(2)$ K
$\alpha = 93.375(3)°$	$0.54 \times 0.47 \times 0.41$mm
$\beta = 106.924(3)°$	

The single crystal measurements of **1** indicate that the piperidine ring adopts a chair conformation. The nitroso group at position 1 has a bisectional orientation. The two aryl rings and the isopropyl group attached to the piperidine ring in positions 2, 6 and 3 respectively, have axial orientations.

Geometry optimization was done for all the conformers of **1-2** as shown in Schemes 1 and 2 according to Dmol^3 method [22]. The calculated relative formation energies of various conformers of **1-2** are displayed in table 4. These values also indicate the high energy conformers **CE** and **B6** for **1-2**. The favored conformation is predicted to be **CA** for the *anti* isomer and **B5** for the *syn* isomer.

Table 3 V*icinal* coupling constants (Hz) in 1–2and their parent compound 3-4.

Comp.		$J_{5,6}$	J_{CH,CH_3}	$J_{H(3),H(7)}$	$J_{2,3}$	$J_{5,5(gem)}$
1	*syn* (major)	7.14, 3.61	6.81, 6.71	9.48	–	–
	anti (minor)	13.47[b]	6.54, 6.72	9.39	–	–
2	*syn* (minor)	7.10, 3.58	6.80, 6.71	9.45	–	–
	anti (major)	13.37[b]	6.52, 6.71	9.36	–	–
3		11.10	7.00, 7.00	–	10.50	–
4		11.25,2.75	7.00, 7.00	–	10.50	–

[a] Frequency of only one line is given by computer; [b] total width of H(6) signal.

Table 4 Calculated relative formation energies (kCal/mol) of various conformers of 1–2.

Comp.	Conformers	CE	CA	B1	B2	B3	B4	B5	B6
1	*syn* (minor)	2.37	0.20	1.06	0.03	0.03	3.32	0	a
	anti (major)	4.73	0	0.22	0.55	0.54	0.22	0.41	4.86
2	*syn* (minor)	2.35	0.20	1.06	0.03	0.03	3.31	0	a
	anti (major)	4.72	0	0.22	0.53	0.53	0.20	0.41	4.86

[a] Did not converge.

3.2. Conformation of isopropyl group at C(3) in 1–4

There are three possible conformations for isopropyl group at C(3) as shown in figure 7. In conformation **A**, the methine proton of isopropyl group at C(3) [H(7)] is *gauche* to C(2) whereas in **C** it is *anti* to H(3) i.e., *gauche* to both C(2) and C(4). In **B**, the methine proton of isopropyl group at C(3) is *gauche* to C(4). Geometry optimization was done for all the conformers shown in figure 7 according to Dmol^3 method for **3**. From the relative heat of formations [**A** (0), **B** (1.13) and **C** (3.09) kCal/mol] it is inferred that the stable conformation in **3** is **A** in which H(7) is *gauche* to C(2). However in the solid state the favored conformation is predicted to be **B** from the observed torsional angles of 78.8° and 49.6° for C2–C3–C31–C32 and C2–C3–C31–C33 (XRD). These torsional angles suggest that both the methyl groups of isopropyl moiety must be *gauche* to C(2) side and hence the methine proton of isopropyl moiety [H(7)] must be *gauche* to C(4) only.

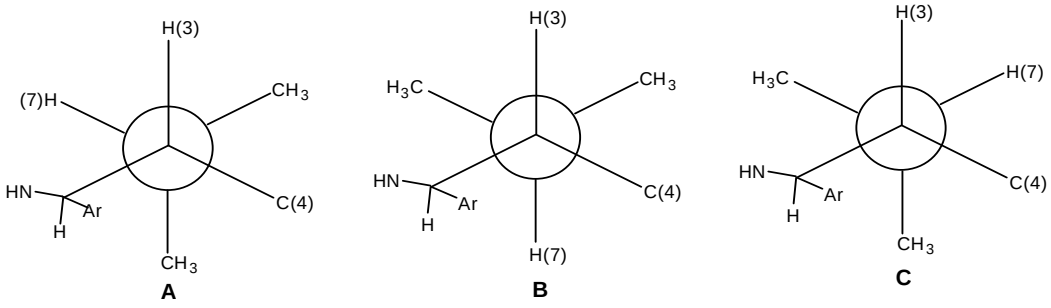


Figure 7. Possible conformations of isopropyl group.

In conformations **A** and **C** only small coupling around 4 Hz is expected for $J_{H(3),H(7)}$. The observed large coupling $J_{H(3),H(7)}$ (9.7–10.4 Hz) in **1–2** supports that H(3) should be *anti* to H(7) and hence predicts conformation **C** in which H(3) is *gauche* to both the methyl groups. In this conformation, the H(3) proton experiences shielding due to magnetic anisotropic effect of both the methyl groups. The XRD measurements however indicate that the proton H(7) is *gauche* to C(2) side [conformation **A**] in **1**.

3.3. Analysis of chemical shifts

Comparison of the chemical shifts of *N*- nitrosation derivatives **1** and **2** with those of the corresponding parent piperidin-4-ones **3-4** reveals that the replacement of –NH by –N-NO group deshields all the heterocyclic ring protons and most of the protons of isopropyl group at C(3). Table 5 reveals the deshielding magnitude observed due to *N*-nitrosation in these derivatives.

Table 5 Observed ^{1}H deshielding/shielding magnitude (ppm) in 1–2[$_{N\text{-nitroso}}$– δ_{NH}].

Comp.		H(2)	H(3)	H_{5e}	H_{5a}	H(6)	Alkyl protons	
							CH	CH_3
1	*syn* (major)	2.78	0.10–0.21	0.52–0.60	-	2.35	0.10	0.03, 0.05
	anti (minor)	2.51	0.32–0.43	0.17–0.26	-	2.15	0.27	0.12, 0.13
2	*syn* (minor)	2.74	0.03–0.10	0.57-0.59	-	2.33	0.04	0.04, 0.06
	anti (major)	2.47	0.20–0.27	0.27-0.23	-	2.14	0.24	0.12, 0.16

'+' Denotes deshielding; '–' denotes shielding.

The magnitude of deshielding observed on the *syn* α protons i.e., H(2) in the *syn* isomer and H(6) in the *anti* isomer ranges from +1.4 to +2.8 ppm in **1–2** and this is considerably higher than the *syn* α axial protons in the normal chair conformation [17,19]. Moreover, the deshielding magnitude observed on *anti* α protons [H(2) in the *anti* isomer and H(6) in the *syn* isomer] is also higher (1.4–2.6 ppm) in **1–2** compared to the *anti* α axial protons in the normal chair conformation. Thus, the observed deshielding of α protons is inconsistent with the normal chair conformation **CE** thus supporting an equilibrium mixture of boat conformation **B1**/**B5** and alternate chair form **CA** for **1–2**.

The chemical shifts of β hydrogens are not expected to be altered significantly due to *N*-nitrosation in normal chair conformation [17,19]. The deshielding magnitude observed on H(5) in **1–2** due to *N*-nitrosation is probably due to the change in the conformation. Similar deshielding magnitude has been observed recently [7,17,19] in some *N*-acyl-*t*(3)-isopropyl-r(2),*c*(6)-bis-2′-furylpiperidine derivatives for which boat conformations have been suggested. Thus, the ^{1}H chemical shift data of **1–2** are also in accordance with the conclusions derived from coupling constants. It is already reported that *syn* α and *anti* α carbons are shifted to upfield by ≈7 and 2 ppm respectively in normal chair conformation due to the replacement of NH by N–NO group in piperidines[7,17,19]. Considerable shielding can be observed on *syn* α carbons only when α hydrogens are present in the same plane of *N*-nitroso moiety. Comparison of ^{13}C chemical shifts of *N*-nitroso derivatives **1–2** with those of parent piperidin-4-ones **3-4** reveals that considerable shielding is observed on α carbons due to *N*-nitrosation. This supports that α hydrogens should lie in the same plane of N–N=O moiety and hence predicts conformations other than normal chair conformation for **1–2**. In alternate chair form **CA** and boat conformation **B1**/**B5** in schemes 1–2 considerable shielding is expected on α carbons since the α hydrogens lie in the same plane of the N–NO moiety. The shielding magnitude observed in *N*-nitroso derivatives **1–2** due to *N*-nitrosation are displayed in table6.

Table 6. Observed ^{13}C deshielding/shielding magnitude (ppm) in 1–3 [$_{N\text{-nitroso}}$– δ_{NH}].

Comp.		C(2)	C(3)	C(4)	C(5)	C(6)	Alkyl carbons	
							CH	CH_3
1	*syn* (major)	–12.23	–1.64	0.20	–8.81	–0.30	3.00	0.58, 2.24
	anti (minor)	–1.40	–2.01	–0.28	–8.81	–9.43	2.57	-0.26, 2.45
2	*syn* (minor)	–12.23	–1.67	0.05	–10.66	–0.48	3.12	0.67, 2.18
	anti (major)	–1.41	–2.05	–0.32	–10.68	–9.60	2.68	-0.14, 2.41

'+' Denotes deshielding; '–' denotes shielding.

Table 6 reveals that the shielding magnitude observed on *syn* α carbons in **1–2** are considerably higher than the values observed in normal chair conformation **CE** and lower than the values observed in the alternate chair conformation **CA** [7,17,19]. The magnitude of shielding observed on C(3) are considerably lower than that observed on C(5) indicating different conformations of isopropyl groups at C(3) in *N*-nitroso derivatives **1–2** compared to the corresponding parent 3-isopropylpiperidin-4-ones **3-4** [equatorial configuration of isopropyl group at C(3)]. For one of the methyl carbons of isopropyl group and C(4) carbons (γcarbons) considerable deshielding has been observed due to *N*-nitrosation. The observation of considerable deshielding for these carbons also supports other than normal chair conformation for **1–2**.

4. Conclusion

Spectral studies reveal the presence of two rotameric forms (*syn* and *anti*) in solution for the two *N*-nitroso-*t*(3)-isopropyl-r(2),*c*(6)-bis(*p*-halo-phenyl)piperidin-4-ones **1–2**. From the coupling constants and the ^{1}H and ^{13}C chemical shift data of *N*-nitroso derivatives **1–2** the favored conformations are predicted to be an equilibrium mixture of boat conformations **B5**/**B1** and alternate chair conformation **CA**. Theoretical calculations also support this observation in majority of cases.

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