IJCRCPS

International Journal of Current Research in Chemistry and Pharmaceutical Sciences
www.ijcrcps.com *Volume 1 Issue 1. 2014 Pages: 37-44*
(pISSN: 2348 – 5213; eISSN: 2348 - 5221)

RESEARCH ARTICLE

SYNTHESIS, SPECTRAL AND COMPUTATIONAL STUDIES OF SOME *N*-SUBSTITUTED *t*(3)-ISOPROPYL-*r(2),c*(6)-BIS(*P*-CHLOROPHENYL) PIPERIDIN-4-ONES

S. SIVAKUMAR[1,*] AND A. MANIMEKALAI[2]

[1]Department of Chemistry, Sri Manakula vinayagar engineering College, Madagadipet, Pondicherry, India
[2]Department of Chemistry, Annamalai University, Annamalainagar 608 002, India
.
Corresponding Author: siva_avc@rediffmail.com

Abstract

Two *N*-acyl-*t*(3)-isopropyl-r(2),*c*(6)-bis(*p*- chlorophenyl)piperidin-4-ones **1–2** and their parent piperidin-4-one **3** were synthesized and the high resolution ^{1}H and ^{13}C NMR spectra have been recorded and analyzed. 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. The effect of varying the substituents at nitrogen on the ^{1}H and ^{13}C chemical shifts has been analyzed in detail.

Keywords: *N*-Substitutedpiperidin-4-ones; Spectral; Computational studies

Introduction

Many piperidine derivatives are found to possess pharmacological activity and form an essential part of the molecular structures of important drugs (Rubiralta et al., 1991; Venkatasa Perumal et al., 2001). Recently attention has been focussed on the application of the piperidone derivatives as prospective biophotonic materials (Nesterov et al., 2003; Sampathkumar et al., 2005). Since the pharmacological properties and the reactivity depend on their stereochemistry, efforts were made for the development of new synthetic techniques leading to stereo selective piperidines and their characterization (Garcia et al., 2004; Diwischek et al., 2005). 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 (Manimekalai A and Sivakumar S 2010; Ravindran et al., 2002; Gdaniec et al., 1995; Pandiarajan et al., 1997; Srinivasan et al., 2004; Vijayalakshmi et al., 2006; Aridoss et al., 2007; Venkatraj et al., 2008; Thiruvalluvar et al., 2006; Jayabharathi et al., 2006; Manimekalai et al., 2007). 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*-acyl- r(2),*c* (6)- bis (*p*-chlorophenyl)-*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

IJCRCPS

International Journal of Current Research in Chemistry and Pharmaceutical Sciences
www.ijcrcps.com Volume 1 Issue 1. 2014 Pages: 37-44
(pISSN: 2348 – 5213; eISSN: 2348 - 5221)

spectroscopy. The preferred conformations were further confirmed by means of conformational analysis performed by Dmol[3] calculations.

Experimental details

Preparation of compounds

The compound *t*(3)-isopropyl-r(2),*c*(6)-bis(*p*-chlorophenyl)piperidin-4-one **3** was prepared according to the procedure described in literature (Manimekalai et al., 2007). It was recrystallized twice from benzene-petroleum ether mixture. Yield: 9.6 g (calc. 13.65 g); m.p: 181–183°C. The *N*-acyl derivatives **1** and **2** were prepared from **3** by adopting the general procedure described in the literature (Manimekalai et al., 2007). The products were recrystallized twice from petroleum ether. The yields were in the range 50–70%. The compounds melted at 204 and 168°C respectively. IR (cm^{-1}): (**1)**; 3238.36, 3052.05, 2953.42, 2927.05, 2674.11, 2557.95, 1791.78, 1686.10, 1592.27, 1489.36, 1423.38, 1321.19, 1174.57, 1090.09, 1012.54, 928.91, 849.62 and 760.30. (**2)**; 3343.98, 3164.19, 2963.23, 2923.51, 1634.18, 1504.25, 1418.73, 1346.22, 1297.03, 1258.14, 1141.42, 1077.97, 1014.52, 951.81, 817.88 and 737.77.

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.

Results and discussion

The high resolution ^{1}H and ^{13}C NMR spectra of *N* – formyl - *t*(3) - isopropyl-r (2), *c*(6)-bis(*p*-chlorophenyl)piperidin-4-one (**1**), *N*-benzoyl-*t*(3)-isopropyl-r(2),*c*(6)-bis (*p*-chloro-phenyl) piperidin -4-one (**2**), and their parent compound *t*(3)-isopropyl-r(2),*c*(6)-bis(*p*-chlorophenyl)piperidin-4-one (**3**) have been recorded in $CDCl_3$ and analyzed. The structures of the synthesized compounds **1–3** are indicated in figure 1. The ^{1}H NMR spectra of *N*-acyl-*t*(3)-isopropyl derivatives **1** and **2** contained two distinct signals for each ~ protons at room temperature. The observation of two sets of signals in **1–2** suggests the presence of restricted rotation around N–C bonds and establishment of equilibrium between two rotamers with coplanar orientation of *N* - acyl group in these derivatives. The two rotamers are labeled as *syn* [carbonyl oxygen is *syn* to isopropyl group at C(3)] and *anti* [carbonyl 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. 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*-acyl derivative 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* ~ protons (*syn* with respect to carbonyl oxygen) are deshielded to a greater extent than the *anti* ~ protons (*anti* with respect to carbonyl oxygen) due to *N*-acylation [7,17]. In the parent *t*(3)-isopropylpiperidin-4-one **3** 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*]. The coupling

IJCRCPS

International Journal of Current Research in Chemistry and Pharmaceutical Sciences
www.ijcrcps.com Volume 1 Issue 1. 2014 Pages: 37-44
(pISSN: 2348 – 5213; eISSN: 2348 - 5221)

constants and the chemical shifts [^{1}H and ^{13}C] of **1–3** are given in tables 1–3.

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-one **3** reveals that this compound adopts normal chair conformation with the equatorial orientations of *p*-chlorophenyl 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. The crystal data are given below.

Crystal data	
$C_{20}H_{21}Cl_2NO$	V = 1771.66(13) Å^3
M_r = 362.28	Z = 4
Monoclinic, $P2_1/c$	MoK~ radiation
a = 17.3013(7) Å	« = 0.37 mm^{-1}
b = 8.3742(4) Å	T = 200 K
c = 12.3687(5) Å	0.49 × 0.39 × 0.15 mm
= 98.647(4)°	

The coupling constants about C(2)–C(3) bonds in both the *syn* and *anti* isomers of *N*-formyl derivative **1** are found to be very small (<1 Hz) [singlet for H(2)]. The observation of only one coupling [7.55 Hz (*syn*), 7.93 Hz (*anti*)] about C(5)–C(6) bond is in contrast to the values observed in the parent piperidin-4-one **3**. These observations cannot be accounted by normal chair conformation **CE** with equatorial orientations of all the substituents. Moreover in the normal chair conformation, severe pseudoallylic [$A^{1,3}$] strain exists between the *N*-formyl group and equatorial *p*-chlorophenyl rings at C(2) and C(6). There are several examples in literature. for which predictable conformational changes for the piperidine ring due to severe $A^{1,3}$ strain have been observed. In order to relieve $A^{1,3}$ strain, the *N*-formyl derivative **1** may adopt alternate chair form or boat form. The possible conformations for the *syn* and *anti* isomers of **1** are shown in schemes 1 and 2 respectively.

In conformations **CE**, **B3** and **B6** in scheme 1 and **CE**, **B4** and **B6** in scheme 2 allylic strain exists between N–C=O group and *p*-chlorophenyl rings at C(2) and C(6) and hence ruled out. The conformation **B2** in scheme 1 and **B2** and **B3** in scheme 2 are also ruled out since in this conformation $J_{2,3}$ is expected to be around 10 Hz which is in contrast to the singlet observed for H(2) in **1**. Molecular mechanics calculations of several *N*-formyl-*trans*-3-alkyl-*cis*-2,6-diphenylpiperidin-4-ones [21] have shown that the boat form **B4** with alkyl group at flagpole position is having higher energy when compared to alternate chair form **CA** and boat forms **B1** and **B5**. Therefore in the present study, the boat conformation **B4** is also ruled out. The singlet observed for H(2) can be accounted by all the three remaining conformations **CA**, **B5** and **B1**. In alternate chair form **CA** both couplings about C(5)–C(6) bond are expected to be around 3–4 Hz. In boat form **B1** the *trans* and *cis* coupling about C(5)–C(6) bond are expected to be around 10–11 and 3–4 Hz respectively. However in the other boat form **B5**, the *trans* and *cis* coupling about C(5)–C(6) bond are expected to be around 4 and 10 Hz respectively. The observation of only one coupling [7.55 (*syn*), 7.93 (*anti*) Hz] about C(5)–C(6) bond suggests that *N*-formyl-3-isopropyl derivative **1** cannot exists in single conformation. It can exists as an equilibrium mixture of two or three conformers. The observed large coupling about C(5)–C(6) bond suggests that the major conformer cannot be **CA** and it may be boat form **B1** or **B5**. An equilibrium mixture of boat forms **B1** and **B5** is ruled out in the present study based on the following observations.

The *trans* coupling about C(5)–C(6) bond in the boat forms **B1** and **B5** are expected to be around 10 and 4 Hz and the *cis* coupling are expected to be around 4 and 10 Hz respectively. An equilibrium mixture of boat forms **B1** and **B5** suggests that both couplings about C(5)–C(6) bond are expected to be almost the same and in the region 5–8 Hz. However, the observation of only one coupling (other coupling is of very small magnitude ≈1

IJCRCPS

International Journal of Current Research in Chemistry and Pharmaceutical Sciences
www.ijcrcps.com Volume 1 Issue 1. 2014 Pages: 37-44
(pISSN: 2348 – 5213; eISSN: 2348 - 5221)

Hz) ruled out the possibility of existing as an equilibrium mixture of boat forms **B1** and **B5**. Therefore both the *anti* and *syn* isomers of **1** exist as an equilibrium mixture of alternate chair form **CA** and boat form **B5**/**B1**.

In alternate chair form **CA** and boat form **B5**, 1,3-*syn* diaxial interaction exists between aryl rings at C(2) and C(6), whereas in boat form **B1** such interaction is absent. The boat form **B1** with *p*-chlorophenyl ring at flagpole position is however expected to have higher energy due to the presence of bulky chloro group in the *para* position of phenyl ring at C(2). Therefore the energies of **CA**, **B1** and **B5** are expected to have comparable magnitude. Therefore the decision of contribution of either the boat form **B5** or **B1** to the equilibrium with alternate chair formation **CA** cannot be made in a reasonable manner in the present investigation. Therefore, it is concluded that the *syn* and *anti* isomers of *N*-formyl-3-isopropylpiperidine derivative exists as an equilibrium mixture of boat form **B1** (J_{trans} ≈10 Hz, J_{cis} ≈4 Hz)/**B5** (J_{trans} ≈4 Hz, J_{cis} ≈10 Hz) and alternate chair form **CA** (both J_{trans} and J_{cis} ≈3–4 Hz). Such an equilibrium mixture suggests that one coupling should be small and another coupling should be around 6–8 Hz depending upon the population.

The closely related *N*-benzoyl derivative **2** is also expected to exist as an equilibrium mixture of boat conformation **B1**/**B5** and **CA** only since the chemical shifts of **2** are closer to **1** rather than the parent compound **3**. The favored conformations predicted from coupling constant analysis of the *N*-acyl derivatives **1–2** are given in Figure 4.

For the *N*-acyl derivatives **1** and **2** geometry optimizations were done for the other six conformers i.e., except **CE** and **B6** only. The relative heat of formations determined for **1** and **2** are also displayed in table 4. From table 4 it is inferred that the minimum energy conformer is **B5** for the *syn* isomer of **2** and **B2** for the *syn* isomer of **1**. For the *anti* isomers theoretical calculation predicts **B1** as the favored conformation in **1** and **B2** in **2**. The conformation **B2** predicted for the *syn* isomer of **1** and *anti* isomer of **2** is in contradictory to the conclusions derived from coupling constants. However for other cases atleast one conformer can be predicted to a reasonable accuracy using theoretical calculations.

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

There are three possible conformations for isopropyl group at C(3) as shown in figure 5. 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 5 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).

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

Comp.		H(2)	H(3)	H_{5e}	H_{5a}	H(6)	Alkyl protons		Other protons
							CH	CH_3	
1	*syn* (major)	6.05 (s)	2.67 (d)	3.13 (dd)	2.80–2.74	5.50 (d)	2.03 (m)	1.04 (d) 0.86 (d)	7.12 (d), 7.05 (d), 7.04 (d), 6.94 (d), 8.71 (CHO), 8.72 (CHO)
	anti (minor)	5.43 (s)	2.70 (d)	3.03 (dd)	2.80–2.74	5.92 (d)	1.97 (m)	1.05 (d) 0.86 (d)	
2	*syn* (minor)	6.34 (s)	2.65 (d)	2.94–2.84		5.51 (s)	2.08 (s)	0.98 (d) 0.75 (d)	6.88 (d), 7.58 (d), 7.04 (d), 7.13 (t), 6.62–6.59
	anti (major)	6.62–6.59	2.79 (d)	2.94–2.84		5.51 (s)	2.23 (s)	1.24 (d) 1.09 (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)

IJCRCPS

International Journal of Current Research in Chemistry and Pharmaceutical Sciences
www.ijcrcps.com Volume 1 Issue 1. 2014 Pages: 37-44
(pISSN: 2348 – 5213; eISSN: 2348 - 5221)

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

Comp.		C(2)	C(3)	C(4)	C(5)	C(6)	Alkyl carbons		Other carbons
							CH	CH_3	
1	*syn* (major)	51.06	58.14	210.09	40.95	55.71	27.96	20.99 20.01	127.66, 127.78, 128.53, 128.88 128.99, 129.26, 163.88 (CHO), 164.08 (CHO)
	anti (minor)	57.91	57.58	209.83	40.62	49.99	27.96	20.47 19.72	
2	*syn* (minor)	52.47	61.00	209.23	≈41.8	59.61	27.85	21.83 ≈20.40	128.99, 129.26, 130.02, 130.68, 132.79, 135.58, 137.63, 138.57, 172.94 (COC_6H_5), ≈174.0 (COC_6H_5)
	anti (major)	53.70	59.06	210.31	41.73	57.48	29.51	20.48 21.83	
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

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

Comp.		$J_{5,6}$	J_{CH,CH_3}	$J_{H(3),H(7)}$	$J_{2,3}$	$J_{5,5(gem)}$
1	*syn* (major)	7.55	6.50, 6.35	10.00	–	15.55
	anti (minor)	7.93	7.15, 6.35	10.51	–	15.63
2	*syn* (minor)	–	a	9.20	–	–
	anti (major)	–	5.65, 6.01	10.07	–	–
3		11.00	7.00, 7.00	–	10.50	–

[a] Frequency of only one line is given by computer;

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* (major)	–	1.01	1.57	0	0.18	1.64	0.09	–
	anti (minor)	–	0.40	0	0.52	0.51	2.61	0.56	–
2	*syn* (minor)	–	1.04	0.97	0.05	0.03	4.48	0	–
	anti (major)	–	2.45	0.85	0	0.11	0.85	0.05	–

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

Comp.		H(2)	H(3)	H_{5e}	H_{5a}	H(6)	Alkyl protons	
							CH	CH_3
1	*syn* (major)	2.07	0.04–0.15	0.50–0.60	0.17–0.22	1.42	0.38	0.01, –0.03
	anti (minor)	1.45	0.07–0.18	0.40–0.51	0.17–0.22	1.84	0.32	0.02, –0.03
2	*syn* (minor)	2.36	0.02–0.13	0.31–0.42	0.21–0.32	1.43	0.43	–0.05, –0.14
	anti (major)	2.64–2.61	0.16–0.27	–	–	1.43	0.58	0.21, 0.20

[a] '+' Denotes deshielding; '–' denotes shielding.

Table 6 Observed ^{13}C deshielding/shielding magnitude (ppm) in **1–2** [$\delta_{N\text{-acyl}} - \delta_{NH}$].

Comp.		C(2)	C(3)	C(4)	C(5)	C(6)	Alkyl carbons	
							CH	CH_3
1	*syn* (major)	–12.78	–2.25	2.24	–9.14	–5.33	1.95	–0.09, 2.37
	anti (minor)	–5.93	–2.81	1.98	–9.47	–11.05	1.95	–0.43, 2.08
2	*syn* (minor)	–11.37	0.61	1.38	≈ –8.29	–1.43	1.84	0.93, ≈2.76
	anti (major)	–10.14	–1.33	2.46	–8.36	–3.56	3.50	–0.42, 4.19

[a] '+' Denotes deshielding; '–' denotes shielding

IJCRCPS

International Journal of Current Research in Chemistry and Pharmaceutical Sciences
www.ijcrcps.com *Volume 1 Issue 1. 2014 Pages: 37-44*
(pISSN: 2348 – 5213; eISSN: 2348 - 5221)

Figure 1. Structures of synthesized compounds **1–3**. **Figure 2.** *Syn* and *anti* rotamers of **1–2**

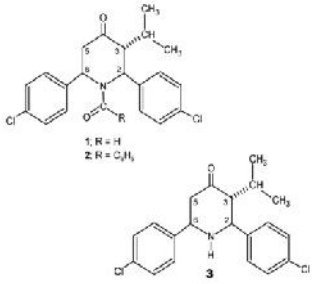


Figure 1

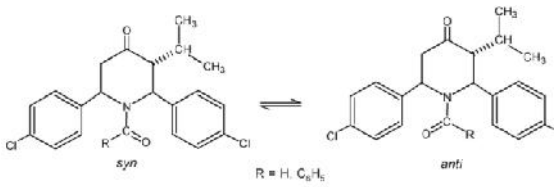


Figure 2

Figure 3. ORTEP structure of **3**

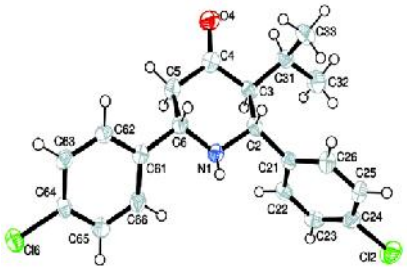


Figure 3

Figure 4. Favored conformations of **1–2**.

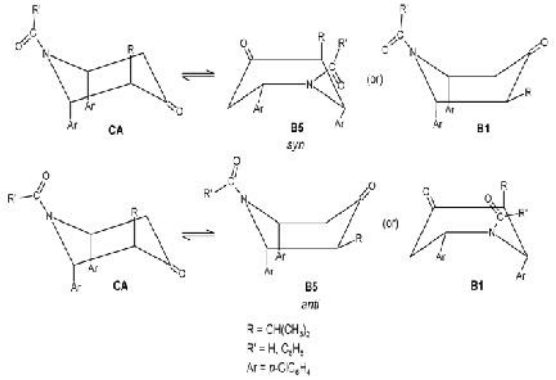


Figure 4

Figure 5. Possible conformations of isopropyl group. **Scheme 1.** Possible conformations for the *syn* isomer of **1**

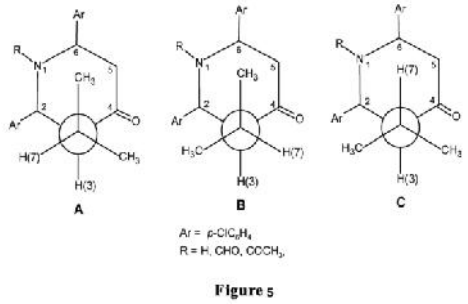
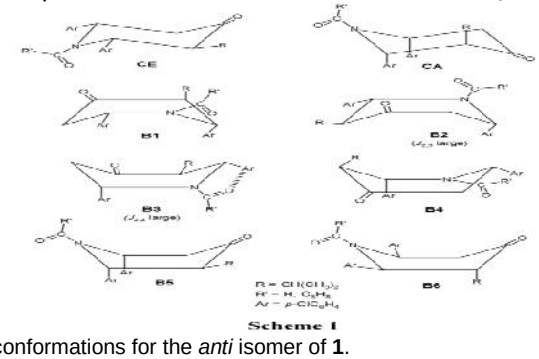
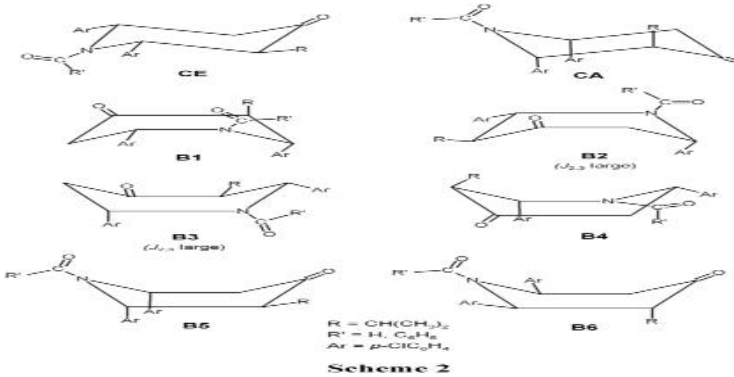


Figure 5



Scheme 1

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



Scheme 2

IJCRCPS

International Journal of Current Research in Chemistry and Pharmaceutical Sciences
www.ijcrcps.com Volume 1 Issue 1. 2014 Pages: 37-44
(pISSN: 2348 – 5213; eISSN: 2348 - 5221)

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 groupsof 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.

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.

Analysis of chemical shifts

Comparison of the chemical shifts of *N*-acyl derivatives **1** and **2** with those of the corresponding parent piperidin-4-one **3** reveals that the replacement of –NH by –NCOR 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*-acylation in these derivatives.

The magnitude of deshielding observed on the *syn* ~ 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* ~ axial protons in the normal chair conformation (Manimekalai et al., 2007; Thangamani et al., 2009).. Moreover, the deshielding magnitude observed on *anti* ~ 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* ~ axial protons in the normal chair conformation. Thus, the observed deshielding of ~ 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 hydrogens are not expected to be altered significantly due to *N*-acylation in normal chair conformation (Manimekalai et al., 2007; Thangamani et al., 2009).. The deshielding magnitude observed on H(5) in **1–2** due to *N*-acylation is probably due to the change in the conformation. Similar deshielding magnitude has been observed recently (Manimekalai et al., 2010, 2007; Thangamani et al., 2009).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* ~ and *anti* ~ carbons are shifted to upfield by ≈7 and 2 ppm respectively in normal chair conformation due to the replacement of NH by NCOR group in piperidines (Manimekalai et al., 2010, 2007; Thangamani et al., 2009). Considerable shielding can be observed on *syn* ~ carbons only when ~ hydrogens are present in the same plane of *N*-acyl moiety. Comparison of ^{13}C chemical shifts of *N*-acyl derivatives **1–2** with those of parent piperidin-4-one **3** reveals that considerable shielding is observed on ~ carbons due to *N*-acylation. This supports that ~ hydrogens should lie in the same plane of N–C=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 ~ carbons since the ~ hydrogens lie in the same plane of the *N*-acyl. The shielding magnitude observed in *N*-acyl derivatives **1–2** due to *N*-acylation are displayed in table 6.

Table 6 reveals that the shielding magnitude observed on *syn* ~ 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** (Manimekalai et al., 2010, 2007; Thangamani et al., 2009). 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*-acyl derivatives **1–2** compared to the corresponding parent 3-isopropylpiperidin-4-one **3** [equatorial configuration of isopropyl group at C(3)]. For one of the methyl carbons of isopropyl group

IJCRCPS

International Journal of Current Research in Chemistry and Pharmaceutical Sciences
www.ijcrcps.com *Volume 1 Issue 1. 2014 Pages: 37-44*
(pISSN: 2348 – 5213; eISSN: 2348 - 5221)

and C(4) carbons (¥ carbons) considerable deshielding has been observed due to *N*-acylation. The observation of considerable deshielding for these carbons also supports other than normal chair conformation for **1–2**.

Conclusion

Spectral studies reveal the presence of two rotameric forms (*syn* and *anti*) in solution for the two *N*-acyl-*t*(3)-isopropyl-r(2),*c*(6)-bis(*p*-chloro-phenyl)piperidin-4-ones **1–2**. From the coupling constants and the ^{1}H and ^{13}C chemical shift data of *N*-acyl 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.

Acknowledgement

We thank NMR Research Centre, IISc, Bangalore for providing all the facilities to record NMR spectra.

References

Aridoss G, Balasubramanian S, Parthiban P and Kabilan S 2007 *Spectro-chim. Acta A* 68 1153.

Delley B 1990 *J. Chem. Phys.* 92 508; b) Delley B 2000 *J. Chem. Phys*. 113 7756.

Diwischek F, Arnone M , Engels B and Holzgrabe U 2005 *Tetrahedron* 61 6993.

Garcia A.B, Valdes C and Paz Cabal M 2004 *Tetrahedron Lett*. 45 4357.

Gayathri P, Thiruvalluvar A. Manimekalai A Sivakumar S and Butcher R.J 2008 *Acta Crystallogr.* E 64 01973.

Gdaniec M , Milewska M.J and Polonski T 1995 *J. Org. Chem.* 60 7411.

Jayabharathi J, Manimekalai A, Selvaraj K and Praveena A 2007 *Med. Chem. Res*. 15 452; b) Jayabharathi J, Manimekalai A , Consalata Vani T and Padmavathy M 2007 *Eur. J. Med. Chem.* 42 593.

Jeyaraman R Thenmozhiyal J.C, Murugadoss R and Venkatraj M 1999 *Indian J. Chem*. B 38 325.

Manimekalai A and Sivakumar S 2010 *Spectrochim. Acta A* 75 113.

Manimekalai A Jayabharathi J, Porselvi V.M and Prabha N 2007 *Indian J. Chem.* B 46 681.

Manimekalai A, Selvaraju K and Maruthavanan T 2007 *Indian J. Chem*. B 46 160.

Nesterov V.N, Timofeeva T.V, Sarkisov S.S, Leyderman A, Lee C.Y and Antipin M.Y 2003 *Acta Crystallogr.* 59 605.

Pandiarajan K, Manimekalai A and Kalaiselvi N 1997 *Magn. Reson. Chem.* 35 372.

Ravindran T, Jeyaraman R , Singh M and Murray R.W 1991 *J. Org. Chem*. 56 4833; b) Ponnusamy S, Venkatraj M, Jeyaraman R, Suresh Kumar M, Kumaran D and Ponnuswamy M.N 2002 *Indian J. Chem*. B 41 614.

Rubiralta M, Giralt E and Diel A 1991 *Piperidine Structure, Preparation and Synthetic Applications of Piperidine and its Derivatives*. Elsevier, Amsterdam.

Sampathkumar R, Sabesan R and Krishnan S 2005 *J. Mol. Liq*. 116 1.

Srinivasan M, Perumal S and Selvaraj S 2004 *Magn. Reson. Chem*. 42 1056.

Thangamani A ,Jayabharathi J and Manimekalai A 2009 *J. Struct. Chem*. 4 662.

Thiruvalluvar A, Balamurugan A, Manimekalai A, Selvaraju K and Maruthavanan T 2006 *Acta Crystallogr.* E 62 2005; b) Thiruvalluvar A. Balamurugan A, Manimekalai A, Selvaraju K and Maruthavanan T 2007 *Acta Crystallogr.* E 63 789.

Thiruvalluvar A. Balamurugan S, Butcher R.J, Manimekalai A and Sivakumar S. 2007 *Acta Crystallogr.* E 63 04482.

Venkatasa Perumal R, Adiraj M and Shanmuga Pandian P 2001 *Indian Drugs* 38 156.

Venkatraj M, Ponnusamy S and Jeyaraman R 2008 *Indian J. Chem*. B 47 411.

Vijayalakshmi R , Muthukumar M, Ponnusamy S and Jeyaraman R 2006 *Indian J. Chem.* B 45 2720.