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Conformation of hindered piperidines: Spectroscopic evidence for contribution of boat conformations

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Abstract. High resolution ^{1}H and ^{13}C NMR resonance assignments and conformational assignments were carried out for four *t*(3)-benzyl-*r*(2),*c*(6)-*bis*(aryl)piperidin-4-ones **1–4** and their four *N*-nitroso-*t*(3)-benzyl-*r*(2),*c*(6)-*bis*(aryl)piperidin-4-ones **5–8**. In addition to conventional 1D NMR methods, 2D shift-correlated NMR techniques (^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY) were used for signal assignments. At room temperature the *t*(3)-benzyl-*r*(2),*c*(6)-*bis*(aryl)piperidin-4-ones **1–4** exist in only one isomeric form whereas their *N*-nitroso derivatives **5–8** exist in two isomeric forms. The preferred conformations of both the isomeric forms of nitrosamines were determined by comparison of the spectral data with those of the corresponding parent amines **1–4** and with the aid of substituent parameters. The results indicate the presence of an equilibrium mixture of boat forms $\mathbf{B}_1$ and $\mathbf{B}_2$ for *Z* isomers of **5–8**. For the E isomers of **5–8**, boat form $\mathbf{B}_1$ is predicted to be the major conformer. The piperidin-4-ones **1–4** exist in normal chair conformations with equatorial orientations of all the substituents.

Keywords. NMR; ^{1}H NMR; ^{13}C NMR; conformational analysis; boat forms.

1. Introduction

Many piperidine derivatives are found to possess pharmacological activity and form an essential part of the molecular structure of important drugs.[1] 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 rings and orientations of the substituents in 2,6-dialkyl- and 2,6-diaryl- substituted piperidines[2–4] due to $A^{1,3}$ strain in the normal chair conformation. The relative preference among the various conformers in the conformational equilibria of *N*-nitroso-*r*(2),*c*(6)-diphenylpiperidin-4-ones[5,6] and their derivatives[7], mono- and di-nitroso-*r*(2), *c*(6)-diphenylhexahydro-1,4-diazepin-5-ones[8,9], *N*-nitroso-2-phenyl-*trans*-decahydroquinolin-4-ones[10] and *N*-nitroso-*r*(2),*c*(4)-diaryl-3-azabicyclo[3.3.1] nonan-9-ones[11,12] have been studied in detail. In all these cases conformations which avoid $A^{1,3}$ strain are favoured. Literature survey[5,6] reveals that no systematic work has been done on heavily substituted 2,6-diaryl(di-and tri-substituted phenyl) piperidines having $A^{1,3}$ strain in the chair conformation. Recently we have synthesized and studied their conformational behaviour of some *N*-nitroso-*t*(3)-alkyl-*r*(2),c(6)-bis(2′-furyl)piperidin-4-ones and *N*-nitroso-*t*(3),*t*(5)-dimethyl-*r*(2), *c*(6)-*bis*(2′-furyl)piperidin-4-one using theoretical and spectral studies.[13] In the present study, we have chosen a set of compounds in which crowding is increased gradually in the aryl rings attached to 2 and 6 positions of the piperidine ring. The present investigation deals with the synthesis and stereochemical analysis of a set of *t*(3)-benzyl-*r*(2),*c*(6)-*bis*(aryl) piperidin-4-ones **1–4** and their *N*-nitroso derivatives **5–8** using ^{1}H and ^{13}C NMR spectroscopy and the results are reported here.

2. Experimental

2.1 *Preparation of compounds*

The compounds *t*(3)-benzyl-*r*(2),*c*(6)-*bis*(aryl) piperidin-4-ones **1–4** were prepared according to the procedure reported in the literature.[14] The *N*-nitroso derivatives **5–8** were prepared from **1–4** by adopting the general procedure described in the literature.[5] All the *N*-nitroso derivatives **5–8** were purified by column chromatography using benzene: ethyl ace-

*For correspondence

tate (4 : 1) as eluent. The yields are as follows: 80% (**1**); 78% (**2**); 70% (**3**); 60% (**4**); 85% (**5**); 80% (**6**); 75% (**7**); 70% (**8**) and the melting points are as follows: semisolid (**1**); 83°C (**2**); 130°C (**3**); 81°C (**4**); 166°C (**5**); semisolid (**6**); semisolid (**7**) and semisolid (**8**).

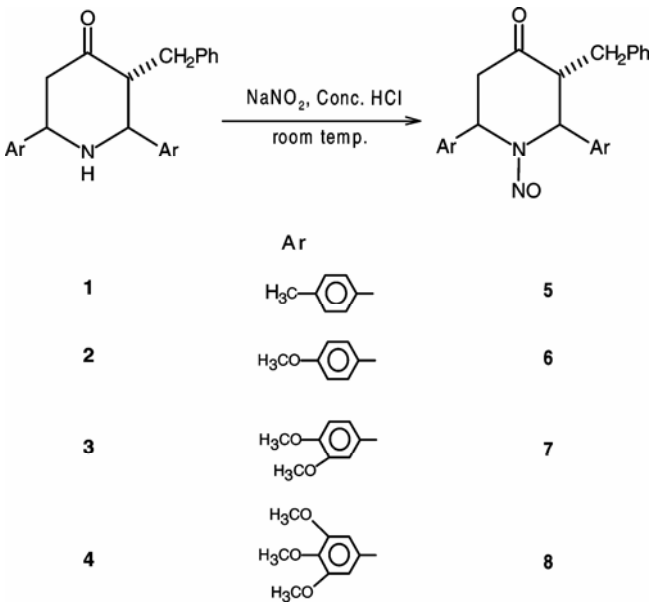
2.2 *Recording of spectra*

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 NMR spectrometer operating at 500·03 and 125·75 MHz for ^{1}H and ^{13}C, respectively. Solutions were prepared by dissolving 10 mg (^{1}H) and 50 mg (^{13}C) of the compound in 0·5 ml of the solvent ($CDCl_3$). All NMR measurements were made on 5 mm NMR tubes. The spectral parameters for ^{1}H were as follows: spectral width 6009·615 Hz, acquisition time 2·726 s, number of data points 32768, digital resolution 0·3 Hz and number of scans 32. For ^{13}C the spectral parameters were as follows: spectral width 27777·777 Hz, acquisition time 0·295 s, number of data points 16384, digital resolution 10·0 Hz and number of scans 64. The phase sensitive of ^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY spectra were recorded on a Bruker DRX 500 NMR spectrometer using standard parameters. For ^{1}H–^{1}H COSY, spectral width 6666·667 Hz, acquisition time 0·154 s, number of data points 2048 and number of scans 16. For ^{1}H–^{13}C COSY, spectral width 6009·615 Hz, acquisition time 0·085 s, number of data points 1024 and number of scans 16.

3. Results and discussion

The high resolution ^{1}H and ^{13}C NMR spectra of *t*(3)-benzyl-*r*(2),*c*(6)-*bis*(4-methylphenyl)-piperidin-4-one (**1**), *t*(3)-benzyl-*r*(2),*c*(6)-*bis*(4-methoxyphenyl)piperidin-4-one (**2**), *t*(3)-benzyl-*r*(2),*c*(6)-*bis*(3,4-dimethoxyphenyl)piperidin-4-one (**3**), *t*(3)-benzyl-*r*(2),*c*(6)-*bis*(3, 4, 5-trimethoxyphenyl)-piperidin-4-one (**4**), *N*-nitroso-*t*(3)-benzyl-*r*(2),*c*(6)-*bis* (4-methylphenyl)piperidin-4-one (**5**), *N*-nitroso-*t*(3)-benzyl-*r*(2), *c*(6)-*bis*(4-methoxy-phenyl)piperidin-4-one (**6**), *N*-nitroso-*t*(3)-benzyl-*r*(2),*c*(6)-*bis*(3, 4-dimethoxyphenyl)-piperidin-4-one (**7**) and *N*-nitroso-*t*(3)-benzyl-*r*(2),*c*(6)-*bis*(3,4,5-trimethoxyphenyl)-piperidin-4-one (**8**) (scheme 1) have been recorded in $CDCl_3$ and analysed. The ^{1}H NMR spectra of *N*-nitroso derivatives **5–8** contained two distinct signals for each α proton at room temperature. ^{13}C NMR spectra also reveal the presence of two sets of signals. The observation of two sets of signals in **5–8** suggests the presence of restricted rotation around N–NO bond and establishment of equilibrium between two rotamers with coplanar orientations of nitroso group in these derivatives. The two rotamers are labelled as **Z** (nitroso oxygen is *syn* to benzylic group at C-3) and **E** (nitroso oxygen is *anti* to benzylic group at C-3) isomers (figure 1).

The assignment of proton signals in the two isomers was done based on the results obtained in the ^{1}H–^{1}H COSY spectra. Literature reveals[5,6] that *syn* α protons should be deshielded to a lesser extent than *anti* α protons. Therefore H(2) is expected to resonate at lower frequency in the **Z** isomer relative to the **E** isomer. Based on this among the two sets of signals the set in which H(2) is considerably lower can be assigned to the **Z** isomer. In ^{13}C NMR spectra the two sets of signals can be easily differentiated



Scheme 1. Structure of compounds **1–8**.

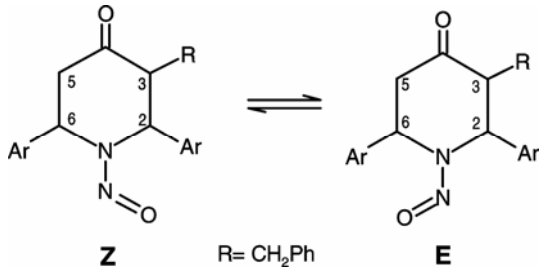


Figure 1. Equilibrium involving *syn* and *anti* rotamers.

Table 1. ^{1}H chemical shifts (ppm) and coupling constant (Hz) **1–8**.

Comp.		H(2)	H(3)	H(5)	H(6)	CH_2Ph	Others	Aromatic protons
1		3·64 (*d*, 9·9 Hz)	2·93–3·04 (*m*)	2·59 (*ax*) (*t*, 12·0 Hz) 2·41 (*eq*) (*dd*, 12·6, 2·9 Hz)	3·94 (*dd*, 11·3, 2·7 Hz)	2·93–3·04 (*m*) 2·30 (*m*)	2·26 2·31	6·95–7·17 7·22–7·32
2		3·70 (*d*, 10·0 Hz)	2·95–3·07 (*m*)	2·68 (*ax*) (*t*, 12·1 Hz) 2·55 (*eq*) (*dd*, 12·7, 2·9 Hz)	4·01 (*dd*, 11·5, 2·6 Hz)	2·95–3·07 (*m*) 2·30 (*d*, 12·9 Hz)	3·77 3·82	6·84–7·09 7·13–7·25 7·27–7·48
3		3·71 (*d*, 10·3 Hz)	3·01 (*t*)	2·72 (*ax*) (*t*, 12·0 Hz) 2·60 (*eq*) (*dd*, 12·8, 2·9 Hz)	4·03 (*dd*, 11·5, 2·8 Hz)	3·09 (*dd*, 13·5, 8·7 Hz) 2·32 (*dd*, 13·8 Hz)	3·86 3·88 3·89 3·90	6·81–6·88 6·95–7·09 7·10–7·16
4		3·69 (*d*, 10·4 Hz)	3·00–3·02 (*m*)	2·72 (*ax*) (*t*, 12·0 Hz) 2·63 (*eq*) (*dd*, 13·0, 3·0 Hz)	4·01 (*dd*, 11·4, 2·6 Hz)	3·14 (*dd*, 13·8, 8·2 Hz) 2·35 (*dd*, 13·6, 2·4 Hz)	3·82, 3·85, 3·86	6·66, 6·67 6·75–7·17
5	**E**	6·23 (*d*, 1·6 Hz)	3·59 (*m*)	2·93 (*dd*, 17·2, 10·3 Hz) 2·75 (*dd*, 17·2, 6·2 Hz)	5·68 (*dd*, 10·3, 6·2 Hz)	3·10 (*dd*, 13·9, 4·2 Hz) 2·63 (*dd*, 13·9, 10·7 Hz)	2·23 2·33	6·68–6·71 6·89–6·95
	Z	5·97 (*d*, 5·9 Hz)	3·38 (*m*)	3·34 (*dd*, 5·3 Hz) 3·03 (*dd*, 17·5, 6·6 Hz)	6·34 (*t*, 11·9 Hz)*	2·84 (*dd*, 13·9, 5·7 Hz) 2·68 (*dd*, 14·0, 7·3 Hz)	2·22 2·32	7·03–7·14 7·18–7·32
6	**E**	6·19 (*d*, 1·3 Hz)	3·57 (*m*)	2·95 (*dd*, 17·1, 9·5 Hz) 2·77 (*dd*, 17·1, 6·5 Hz)	5·78 (*dd*, 9·2, 6·7 Hz)	2·66 (*dd*, 13·8, 10·6 Hz) 3·05–3·11 (m, 4·3 Hz)	3·70 3·78	6·58–6·64 6·70–6·83
	Z	5·97 (*d*, 5·9 Hz)	3·32–3·38 (*m*)	3·32–3·38 (m, 4·5 Hz) 3·05–3·11 (m, 6·9 Hz)	6·37 (*t*, 11·1 Hz)*	2·69 (*dd*, 14·2, 7·3 Hz) 2·83 (*dd*, 13·9, 5·7 Hz)	3·70 3·77	7·03–7·10 7·17–7·32
7	**E**	6·21 (*d*, 1·9 Hz)	3·58–3·61 (*m*)	3·01 (*dd*, 17·2, 9·6 Hz) 2·80 (*dd*, 17·2, 6·5 Hz)	5·80 (*dd*, 9·5, 6·6 Hz)	3·09–3·14 (*m*) 2·65 (*dd*, 13·9, 10·7 Hz)	3·58 3·66	6·49–6·54 6·58–6·64
	Z	5·96 (*d*, 6·2 Hz)	3·36–3·41 (*m*)	3·36–3·41 (m, 4·2 Hz) 3·09–3·14 (*m*)	6·41 (*dd*, 6·7, 4·3 Hz)	2·84 (*dd*, 13·9, 5·7 Hz) 2·68 (*dd*, 14·2, 6·8 Hz)	3·71 3·78 3·84 3·94 3·96	6·73–6·83 6·97–7·03 7·19–7·41
8	**E**	6·23 (s)	3·57–3·61 (*m*)	3·03 (*dd*, 17·0, 8·5 Hz) 2·87 (*dd*, 17·1, 6·8 Hz)	5·94 (*t*, 15·2 Hz)*	3·12 (*dd*, 13·9, 4·6 Hz) 2·65–2·71 (*m*)	3·62 3·63	7·05, 7·07 7·21–7·29
	Z	6·13 (*d*, 4·9 Hz)	3·42 (*dd*)	3·36 (*dd*, 16·9, 3·6 Hz) 3·20 (*dd*, 16·9, 7·2 Hz)	6·45 (s)	2·93 (*dd*, 13·9, 5·8 Hz) 2·65–2·71 (*m*)	3·68 3·71 3·72 3·74 3·77	7·33–7·35

*Total width derived from H(6) signal

based on intensities. Literature study reveals[3,5,6] that *syn* α carbons should be shielded to a greater extent than *anti* α carbons. Therefore C(2) should absorb at higher frequency in the **E** isomer than in the **Z** isomer. Among the two sets of signals for the **E** and **Z** isomers the one in which C(2) is considerably higher is assigned to the **E** isomer. This assignment is further confirmed by recording ^{1}H–^{13}C COSY spectra for **5–8**. The chemical shifts and coupling constants derived from ^{1}H NMR spectra are displayed in table 1. Table 2 reports ^{13}C chemical shifts of **1–8** recorded at room temperature.

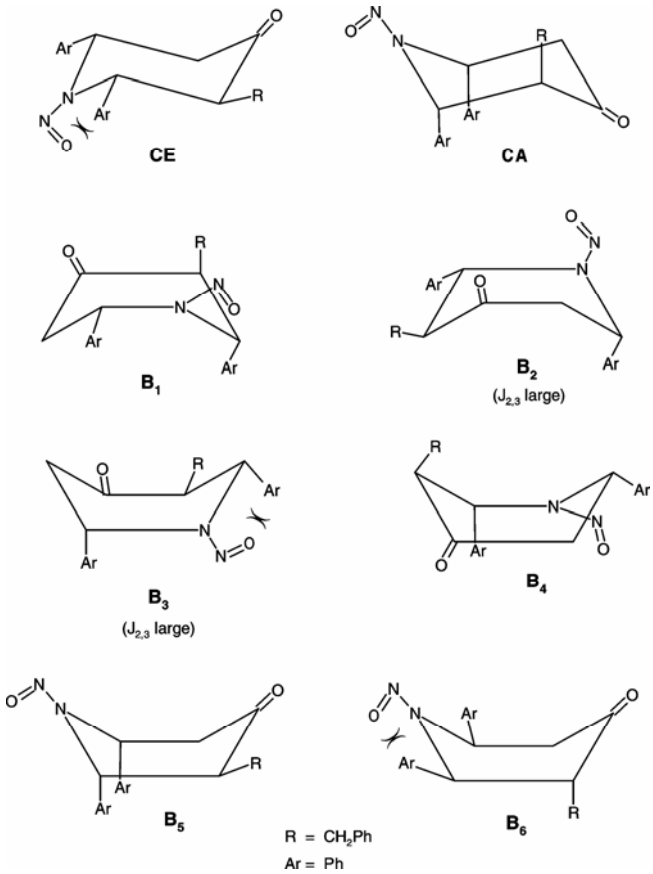
3.1 *Ring conformations*

3.1a *3-Benzylpiperidin-4-ones* **1–4**: The observation of one large (≈ 11 Hz) and one small coupling (≈ 3 Hz) about C(5)–C(6) bond and one large coupling (≈ 10 Hz) about C(2)–C(3) bond in piperidin-4-ones **1–4** reveals that these compounds adopt normal chair conformations with equatorial orientation of aryl rings at C-2 and C-6 and benzylic group at C-3.

3.1b *N-nitroso-3-benzylpiperidin-4-ones* **5–8**: The coupling constants about C(2)–C(3) bond in the **Z**

Table 2. ^{13}C Chemical shifts of **1–8**.

Compound		C(2)	C(3)	C(4)	C(5)	C(6)	CH_2Ph	Others	Aromatic carbons
1		66·97	59·50	208·10	51·40	61·45	30·27	20·98 20·92	141·06–125·39
2		66·47	59·50	208·03	51·30	60·93	30·17	54·92	159·16–113·70
3		67·26	59·80	208·34	51·60	61·62	30·38	55·96	149·18–109·78
4		67·31	60·24	207·43	50·86	61·57	29·97	55·63 58·95	152·80–103·12
5	**E**	61·80	52·52	207·28	43·48	55·07	35·69	20·83 20·89	138·35–126·21
	Z	55·49	53·13	207·06	42·39	60·22	34·59		
6	**E**	61·49	52·93	207·00	42·71	54·68	35·33	54·68 54·83	159·08–113·21
	Z	54·83	53·70	206·77	41·76	59·60	34·26		
7	**E**	61·62	52·64	206·61	42·29	54·79	35·14	55·12 55·23	153·75–108·39
	Z	55·37	53·66	206·41	41·37	59·66	33·84	54·95 55·05	
8	**E**	62·24	52·61	206·93	42·07	53·72	35·69	55·38 55·67	152·86–103·24
	Z	54·91	53·14	206·93	41·30	60·48	34·84		



Scheme 2. Possible conformation of the **Z**-isomers of **5–8**.

isomers of *N*-nitroso-3-benzyl derivatives **5–8** are in the range of 4·9–6·2 Hz. The two couplings observed about C(5)–C(6) bond are in the range of 6·6–7·2 and 3·6–5·3 Hz. The coupling constants are in contrast to the values observed in piperidin-4-ones **1–4** which exist in normal chair conformation with equatorial orientation of all the substituents. In the normal chair conformation severe pseudo allylic ($A^{1,3}$) strain exists between *N*-nitroso group and equatorial aryl rings at C-2 and C-6 in **5–8**. In order to relieve $A^{1,3}$ strain, the *N*-nitroso derivatives **5–8** may adopt alternate chair form or boat form. The possible conformations for the **Z** isomers of **5–8** are shown in scheme 2.

In conformations **CE**, $\mathbf{B}_3$ and $\mathbf{B}_6$ shown in scheme 2, allylic strain exists between N–N=O group and aryl ring and hence these conformations are ruled out in the present study. Moreover, in the conformations $\mathbf{B}_3$ and **CE**, $J_{2,3}$ is expected to be around 10–12 Hz which is in contrast to the lower magnitude observed in the range of 4·9–6·2 Hz in *N*-nitroso-3-benzyl derivatives **5–8**.

Molecular mechanics calculations of several *N*-nitroso-*trans*-3-alkyl-*cis*-2, 6-diphenylpiperidin-4-ones[7] have shown that the boat form $\mathbf{B}_4$ with alkyl group at flagpole position is having higher energy when compared to alternate chair form **CA** and boat

forms $\mathbf{B}_1$, $\mathbf{B}_2$ and $\mathbf{B}_5$. Therefore in the present study, the boat conformation $\mathbf{B}_4$ is also neglected.

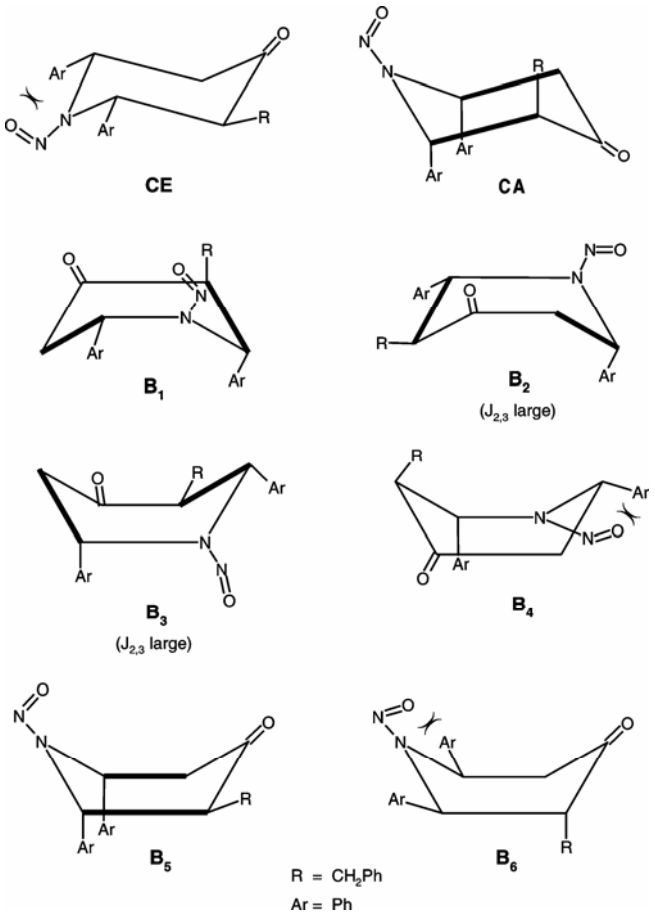
The *trans* and *cis* couplings about C(5)–C(6) bond are expected to be around 10 and 4 Hz in boat form $\mathbf{B}_1$ and 4 and 10 Hz in boat form $\mathbf{B}_5$. However, both the *trans* and *cis* couplings are expected to be lower (3–4 Hz) in the boat conformation $\mathbf{B}_2$ and alternate chair form **CA**. The observed couplings in the range of 6·6–7·2 and 3·6–5·3 Hz about C(5)–C(6) bond in **5–8**, suggest that these compounds cannot exist in single conformation. They may exist as an equilibrium mixture of two or more conformers in solution. The observed coupling around 7 Hz about C(5)–C(6) bond indicates that the major conformer cannot be $\mathbf{B}_2$ and **CA**. The major conformer may be either the boat form $\mathbf{B}_1$ or the boat form $\mathbf{B}_5$. In the boat form $\mathbf{B}_5$, *syn* 1,3-diaxial interaction exists between aryl rings at C-2 and C-6 whereas this interaction does not exist in the boat form $\mathbf{B}_1$. Therefore, the major conformer may be $\mathbf{B}_1$. The observed coupling constants can be accounted for three possibilities: (i) an equilibrium mixture of $\mathbf{B}_1$ and **CA**, (ii) an equilibrium mixture of $\mathbf{B}_1$ and $\mathbf{B}_2$ and (iii) an equilibrium mixture of $\mathbf{B}_1$ and $\mathbf{B}_5$.

In alternate chair form **CA** and boat form $\mathbf{B}_5$ *syn* 1,3-diaxial interaction exists between aryl rings at C-2 and C-6 and hence these forms are destabilized to some extent. However in boat form $\mathbf{B}_2$ such interaction is absent. Therefore, based on coupling constants it is suggested that the **Z** isomers of *N*-nitroso derivatives **5–8** exist as an equilibrium mixture of boat forms $\mathbf{B}_1$ and $\mathbf{B}_2$.

The coupling constants about C(2)–C(3) bond in the **E** isomers of *N*-nitroso-3-benzyl derivatives **5–8** are in the range of 1·3–1·9 Hz. The two couplings observed about C(5)–C(6) bond are in the range of 8·5–10·2 and 6·2–6·8 Hz. The coupling constants are in contrast to the values observed in piperidin-4-ones **1–4** which exist in normal chair conformation with equatorial orientations of all the substituents. In order to relieve $A^{1,3}$ strain, the *N*-nitroso derivatives **5–8** may adopt alternate chair form or boat form. The possible conformations for the **E** isomers of **5–8** are shown in scheme 3.

In conformations **CE**, $\mathbf{B}_4$ and $\mathbf{B}_6$ shown in scheme 3, allylic strain exists between *N*-nitroso group and aryl ring at C-6 and hence these conformations are ruled out in the present study. The conformations $\mathbf{B}_2$ and $\mathbf{B}_3$ are also not possible since in these conformations $J_{2,3}$ are expected to be around 10–12 Hz which is in contrast to the lower magnitude observed in the range of 1·3–1·9 Hz in *N*-nitroso-3-benzyl derivatives **5–8**. The *trans* and *cis* couplings about C(5)–C(6) bond are expected to be around 10 and 4 Hz in boat form $\mathbf{B}_1$ and 4 and 10 Hz in boat form $\mathbf{B}_5$. However, both the *trans* and *cis* couplings are expected to be lower (3–4 Hz) in the alternate chair form **CA**. The observed couplings in the range of 8·5–10·2 and 6·2–6·8 Hz about C(5)–C(6) bond and 1·3–1·9 Hz about C(2)–C(3) bond in **5–8**, ruled out the possibility of existing in alternate chair form **CA**. The observed coupling constants can be accounted by either the highly distorted boat form $\mathbf{B}_1$ or the boat form $\mathbf{B}_5$. In the boat form $\mathbf{B}_5$ *syn* 1,3-diaxial interaction exists between aryl rings at C-2 and C-6 whereas this interaction does not exist in the boat form $\mathbf{B}_1$. Therefore the **E** isomers of **5–8** exist in the highly distorted boat form $\mathbf{B}_1$. A small amount of boat form $\mathbf{B}_5$ to be equilibrium cannot be completely excluded in the present study.

3.1c *Conformation of benzylic group at C(3) in* **1–8**: There are three possible conformations **A**, **B** and



Scheme 3. Possible conformation of the **E**-isomers of **5–8**.

C for the benzylic group at C-3 in **1–4** as shown in figure 2. In conformation **C**, H(3) is *gauche* with respect to both the methylene protons of the benzylic group at C-3 and hence both the coupling constants $J_{H(3),CH2Ph}$ are expected to be around 3–4 Hz. However, in conformations **A** and **B**, one coupling is expected to be around 10–12 Hz and other coupling is expected to be around 3–4 Hz. In piperidin-4-ones **1–4** the coupling constants extracted are around 3 and 8 Hz. The former corresponds to *gauche* coupling and other value falls in between those for a *gauche* and *anti* coupling. This large coupling suggests that the major conformer may be either **A** or **B**. Moreover in the conformation **C**, two *gauche* interactions exist (phenyl with C(2) and C(4) substituents) whereas in the other forms **A** and **B** only one *gauche* interaction (phenyl with either C-2 or C-4 substituents) is present. Drieding model reveals that in conformation **B**, there will be severe interaction between phenyl ring of the benzylic group at C-3 with the aryl ring at C-2 and hence this conformation is ruled out in the present study. Therefore, the favoured conformation of benzylic group at C-3 in the piperidin-4-ones **1–4** is predicted to be **A**. In conformation **A** the large and small couplings are expected to be 10 and 3 Hz. However, the observed couplings 8 and 3 Hz suggest that a small amount of another conformer, i.e. the conformation **B** may also be present in solution in addition to the major conformation **A**. Among the methylene protons of the benzylic group at C-3, the one that experiences large coupling with H(3) in conformer **A** experience small coupling with H(3) in conformer **B** and *vice versa*. Thus, the conformation of benzylic group in the piperidin-4-ones **1–4** is found to be an equilibrium mixture of conformers **A** (major) and **B** (minor). In *N*-nitroso-3-benzyl derivatives **5–8** also one can have three conformations **A′**, **B′** and **C′** (figure 3). For the **E** isomer the coupling constants extracted are around 4 and 10 Hz. The former corresponds to *gauche* coupling and other corresponds to *anti* coupling. These couplings ruled out the possibility of existing in the conformation **C′** and suggest that the favourable conformer may be either **A′** or **B′**. Moreover in the conformation **C′**, two *gauche* interactions exists whereas in the other forms **A′** and **B′** only one *gauche* interaction is present. Drieding model reveals that in conformation **B′**, there will be more interaction between phenyl ring of the benzylic group at C-3 with the aryl ring at C-2 and hence this conformation is ruled out in the present study. Therefore, the favoured conformation of benzylic group at C-3 in the **E** isomers of **5–8** is predicted to be **A′**.

In the **Z** isomers of *N*-nitroso-3-benzyl derivatives **5–8**, the coupling constants extracted are around 5 and 7 Hz. The former corresponds to *gauche* coupling and other value falls in between those for a

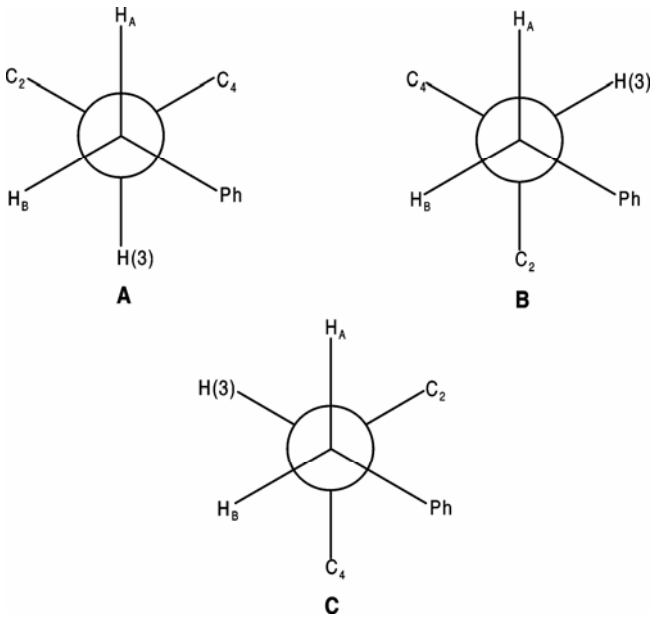


Figure 2. Possible conformations of benzylic group at C(3) in **1–4**.

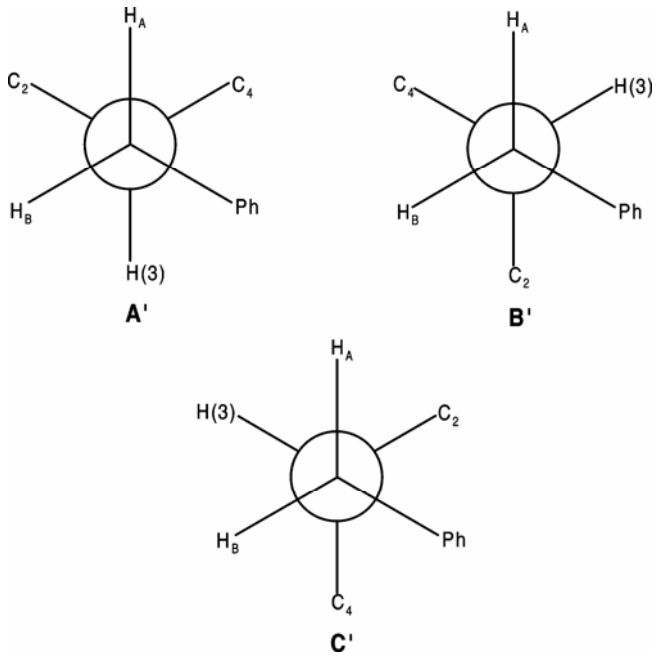


Figure 3. Possible conformations of benzylic group at C(3) in **5–8**.

Table 3. Observed ^{1}H deshielding magnitude (ppm)* in *N*-nitrosopiperidin-4-ones **5–8**.

Compound		H(2)	H(3)	H(5)	H(6)	CH_2Ph
5	**E**	+2·59	+ (0·66–0·55)	+0·34, +0·34	+1·74	–0·30 to –0·41, +0·80
	Z	+2·33	+ (0·43–0·31)	+0·75, +0·62	+2·40	–0·09 to –0·20, +0·38
6	**E**	+2·49	+ (0·62–0·50)	+0·27, +0·22	+1·77	–0·29 to –0·41, 0·75–0·81
	Z	+2·27	+ (0·37–0·31)	+(0·64–0·70), +(0·50–0·56)	+2·36	–0·26 to –0·38, +0·53
7	**E**	+2·50	+ (0·57–0·60)	+0·29, +0·20	+1·77	0 to –0·05, +0·33
	Z	+2·25	+ (0·35–0·40)	+(0·64–0·69), +(0·49–0·54)	+2·38	–0·25, +0·36
8	**E**	+2·54	+ (0·57–0·59)	+0·31, +0·24	+1·93	–0·02, + (0·30–0·36)
	Z	+2·44	+ (0·42–0·40)	+0·64, +0·57	+2·44	–0·21, + (0·30–0·36)

*Calculated relative to compounds **1–4**.

Table 4. Observed ^{13}C shielding and deshielding magnitude (ppm)* in *N*-nitrosopiperidin- 4-ones **5–8**.

Compound		C(2)	C(3)	C(4)	C(5)	C(6)	CH_2Ph
5	**E**	–5·17	–6·98	–0·82	–7·92	–6·38	+5·42
	Z	–11·48	–6·37	–1·04	–9·01	–1·23	+4·32
6	**E**	–4·98	–6·57	–1·03	–8·59	–6·25	+5·16
	Z	–11·64	–5·80	–1·26	–10·04	–1·33	+4·09
7	**E**	–5·64	–7·16	–1·73	–9·31	–6·83	+4·76
	Z	–11·89	–6·14	–1·93	–10·23	–1·96	+3·46
8	**E**	–5·07	–7·63	–0·50	–8·79	–7·85	+5·72
	Z	–12·40	–7·10	–0·50	–9·56	–1·09	+4·87

*Calculated relative to compounds **1–4**

gauche and *anti* coupling. This large coupling suggests that the major conformer may be either **A′** or **B′**. Based on the arguments given for the **E** isomers, the major conformation of benzylic group at C-3 is predicted to be **A′** in the **Z** isomers also. The large and small couplings observed around 7 and 5 Hz suggest that a small amount of another conformer, i.e. the conformation **B′** may also be present in solution in addition to the major conformation **A′**. Thus the conformation of benzylic group in the **Z** isomers of **5–8** is found to be an equilibrium mixture of conformers **A′** (major) and **B** (minor).

3.2 *Analysis of chemical shifts*

Comparison of the chemical shifts of *N*-nitroso derivatives **5–8** with those of the corresponding piperidin-4-ones **1–4** reveal that the replacement of –NH by –N–N=O group deshields most of the heterocyclic ring protons and the observed deshielding magnitude are displayed in table 3. The magnitude of deshielding observed on the *syn* α protons, i.e. H(2) in the **Z** isomer and H(6) in the **E** isomer ranges from +1·7 to 2·4 ppm and this is closer to the values observed for *syn* α-equatorial protons which lie in the same plane of the N–NO moiety. Moreover, the deshielding magnitude observed on *anti* α protons [H(2) in the **E** isomer; H(6) in the **Z** isomer] is also higher [+2·59 to 2·36 ppm] compared to the *anti* α axial protons in the normal chair conformation. Thus, the observed deshielding of α protons are inconsistent with the normal chair conformation **CE** thus supporting conformations in which *syn* α protons lie in the same plane of the N–N=O moiety.

The observed deshielding magnitude of H(3) and H(5) protons in *N*-nitroso derivatives **5–8** due to *N*-nitrosation is probably due to the change in conformation, i.e. an equilibrium mixture of boat forms $\mathbf{B}_1$ and $\mathbf{B}_2$ for **Z** isomers of **5–8** and **E** isomer of **5–8** the boat conformation $\mathbf{B_1}$ only.

Table 4 reveals that the shielding values observed on *syn* α carbons [C(6) in **E** isomer and C(2) in **Z** isomer] are considerably higher than the values observed in normal chair conformation **CE**. However, the magnitude of shielding observed on *anti* α carbons [C(2) in **E** isomer and C(6) in the **Z** isomer] are lower than the values observed in normal chair conformation **CE**. The magnitude of shielding observed on β carbons, i.e. C(3) is considerably lower than those observed on C(5) indicating different configurations of benzylic groups at C(3) in **5–8** compared to the corresponding piperidin-4-ones **1–4**. All these values support other than normal chair conformation for **5–8**, i.e. conformation in which *syn* α hydrogens lie in the same plane of N–NO moiety.

In conclusion, the conformations of **Z** isomers of *N*-nitroso-*t*(3)-benzyl-*r*(2), *c*(6)-*bis*(aryl)piperidin-4-ones **5–8** are established to be an equilibrium mixture of boat forms $\mathbf{B}_1$ and $\mathbf{B}_2$ by ^{1}H and ^{13}C spectral studies and the **E** isomers of **5–8** exist in boat conformation $\mathbf{B}_1$ only.

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