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BOAT FORM CONTRIBUTIONS IN CROWDED PIPERIDINES: THEORETICAL AND EXPERIMENTAL STUDY

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The preferred conformations of *N*-nitroso-*t*(3)-alkyl-*r*(2),*c*(6)-bis(2′-furyl)-piperidin-4-ones **1—3** [alkyl = CH_3, C_2H_5 and $CH(CH_3)_2$] and *N*-nitroso-*t*(3),*t*(5)-dimethyl-*r*(2),*c*(6)-bis(2′-furyl)piperidin-4-one **4** in solutions were assigned by means of ^{1}H and ^{13}C NMR studies. The results derived from NMR spectra indicate the presence of an equilibrium mixture of boat conformation $\boldsymbol{B_1}$ and alternate chair conformation ***CA*** for the ***E*** isomers of **1—3** and ***Z*** isomers of **2—3**. For the ***Z*** isomer of **1** boat form $\boldsymbol{B_2}$ is predicted to be the major conformer. The *N*-nitroso-3,5-dimethyl derivative **4** exists in the boat form $\boldsymbol{B_1}$ only. Conformational analysis performed through semiempirical molecular orbital calculations also supports the conformations for **3—4**. The presence of one conformer in the equilibrium can be predicted to a reasonable accuracy by theoretical studies in **1—2**. The effects due to *N*-nitrosation on ^{1}H and ^{13}C chemical shifts are also interpreted in terms of these conformations. The conformation of isopropyl group at C(3) was also predicted by spectral and theoretical studies.

K e y w o r d s: *N*-nitroso-2,6-bis(2′-furyl)piperidines, conformations, ^{1}H NMR, ^{13}C NMR, semiempirical AM1 calculations.

Many piperidine derivatives are found to possess pharmacological activity [1] and form an essential part of the molecular structure of important drugs [2, 3]. Recently attention has been focused on the application of the piperidone derivatives as prospective biophotonic materials [4, 5]. Since the pharmacological properties and the reactivity depend on their stereochemistry, efforts were made for the development of new synthetic techniques leading to stereoselective piperidines and their characterization [6, 7]. 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 [8—10]. It is also interesting to note that certain nitrosoamines have been reported to possess anticancer activities [11] and blocking the positions α to the ring nitrogen atom by methyl groups in cyclic nitrosoamines reduces the carcinogenic activity [12]. The relations among various conformers in the conformational equilibria of *N*-nitroso-*r*(2),*c*(6)-diphenylpiperidin-4-ones [13, 14] and their derivatives [15], mono- and di-nitroso-*r*(2),*c*(6)-diphenylhexahydro-1,4-diazepin-5-ones [16, 17], *N*-nitroso-2-phenyl-*trans*-decahydroquinolin-4-ones [18] and *N*-nitroso-*r*(2),*c*(4)-diaryl-3-azabicyclo[3.3.1]nonan-9-ones [19, 20] have been studied in detail. In all these cases conformations which avoid $A^{1,3}$ strain are favoured.

In an effort to create new derivatives of pharmacologically active piperidines, the present investigation was undertaken. Synthesis and conformational analysis of some piperidine derivatives which incorporated phenyl rings at C(2) and C(6) positions were reported in our previous studies [21, 22]. So far only a few studies have been carried out on the conformations of piperidine derivatives in which a five-membered ring is incorporated at 2 and 6 positions [23, 24]. Recently a set of new piper-

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idones which incorporated furyl rings at C(2) and C(6) were synthesised and studied in our laboratory [25-27]. In continuation of this work, the synthesis and stereochemical analysis of a set of *N*-nitroso-*r*(2),*c*(6)-bis(2′-furyl)piperidin-4-ones **1—4** were carried out using ^{1}H and ^{13}C NMR spectroscopy in the present study and the results are reported herein. The preferred conformations were further confirmed by means of conformational analysis performed by semiempirical molecular orbital calculations.

EXPERIMENTAL

Preparation of N-nitroso derivatives 1—4. The compounds *t*(3)-alkyl- and *t*(3),*t*(5)-dimethyl-*r*(2),*c*(6)-bis(2′-furyl)piperidin-4-ones **5-8** were prepared according to the procedure reported in the literature [26]. The compounds were recrystallised twice from benzene-petroleum ether mixture. The compounds melted at 40 °C (**5**), 47 °C (**6**), 182 °C (**7**) and 57 °C (**8**). The *N*-nitroso derivatives **1—4** were prepared from **5—8** by adopting the general procedure described in the literature [13, 14]. All the *N*-nitroso derivatives **1—4** were purified by column chromatography using *n*-hexane:ethylacetate mixture (5:1) as eluent. The yields and melting points: **1**, 90 %, 28—30 °C; **2**, 89 %, 91 °C; **3**, 78 %, 142 °C; **4**, 75 %, 80 °C.

Measurements. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 NMR spectrometer operating at 400.13 and 100.62 MHz for ^{1}H and ^{13}C, respectively. Solutions were prepared by dissolving 10 mg (^{1}H) or 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. The spectral parameters for ^{1}H were as follows: spectral width 6756.757 Hz, acquisition time 1.212 s, number of data points 16384, digital resolution 0.3 Hz and number of scans 5. For ^{13}C, the spectral parameters were as follows: spectral width 29411.766 Hz, acquisition time 0.557 s, number of data points 32768, digital resolution 2.0 Hz and number of scans 2084. The phase sensitive ^{1}H—^{1}H and ^{1}H—^{13}C COSY spectra were recorded on a Bruker DRX 400 NMR spectrometer using standard parameters. For ^{1}H—^{1}H COSY, spectral width 6024.096 Hz, acquisition time 0.17 s, number of data points 2048 and number of scans 24. For ^{1}H—^{13}C COSY, spectral width 5081.301 Hz, acquisition time 0.10 s, number of data points 16384 and number of scans 16.

Theoretical calculations. Semiempirical molecular orbital calculations were performed using AM1 Hamiltonian available in Argus lab [28, 29] (version 4.0) on a Pentium personal computers.

RESULTS AND DISCUSSION

The high resolution ^{1}H and ^{13}C NMR spectra of *N*-nitroso-*t*(3)-methyl-*r*(2),*c*(6)-bis-(2′-furyl)piperidin-4-one (**1**), *N*-nitroso-*t*(3)-ethyl-*r*(2),*c*(6)-bis(2′-furyl)piperidin-4-one (**2**), *N*-nitroso-*t*(3)-isopropyl-*r*(2),*c*(6)-bis(2′-furyl)piperidin-4-one (**3**) and *N*-nitroso-*t*(3),*t*(5)-dimethyl-*r*(2),*c*(6)-bis(2′-furyl)piperidin-4-one (**4**) (Fig. 1) have been recorded in $CDCl_3$ and analysed. The spectra were also recorded at low temperatures (–15 and –30 °C). The ^{1}H NMR spectra of *N*-nitroso derivatives **1—3** contained two distinct broad signals for each α proton at room temperature and the signals are well resolved at low temperatures. ^{13}C NMR spectra also reveal the presence of two sets of signals. The observation of two sets of signals in **1—3** suggests the presence of restricted rotation around N—NO bond and establishment of equilibrium between two rotamers with coplanar orientation of nitroso group in these derivatives. The two rotamers are labelled as ***Z*** [nitroso oxygen is *syn* to alkyl group at C-3] and ***E*** [nitroso oxygen is *anti* to alkyl group at C-3] isomers (Fig. 2). The variable temperature NMR spectra of **4** reveal only one set of signals indicating the presence of a single isomer in solution.

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 [13, 14] reveals 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 based on intensities. Literature [9, 13, 14] reveals 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*** iso-

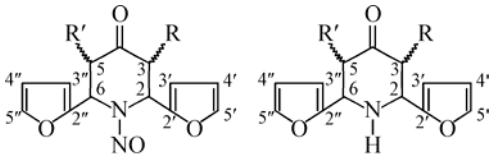


Fig. 1. Structures of **1—8**

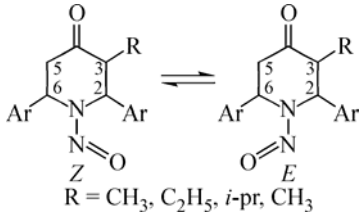
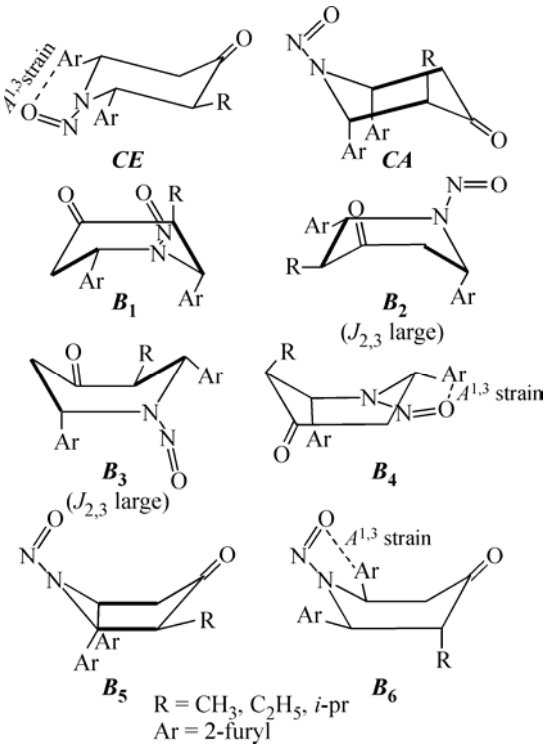


Fig. 2. Equilibrium involving *syn* and *anti* rotamers

mer 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 all the compounds. The chemical shifts and coupling constants derived from –15 °C ^{1}H NMR spectra are displayed in Table 1. Table 2 reports ^{13}C chemical shifts of **1—4** recorded at –15 °C. The chemical shifts and the coupling constants of parent piperidin-4-ones **5—8** (Fig. 1) are also included in these tables for the purpose of comparison.

Ring conformations: *N*-nitroso-3-alkylpiperidin-4-ones 1—3. The *vicinal* coupling constants $J_{H(2),H(3)}$ in the ***E*** isomers of **1—3** are in the range 2.5—4.8 Hz. Moreover only one *vicinal* coupling $J_{H(5),H(6)}$ in the range 4.6—7.7 Hz was observed in the ^{1}H NMR spectra of **1—3**, an exception being **2*E*** for which both the couplings $J_{H(5),H(6)}$ and $J_{H(5)',H(6)}$ are observed. These coupling constants are in contrast to the values observed in parent piperidin-4-ones **5—7** which exist in normal chair conformation with equatorial orientations of all the substituents. In the normal chair conformation severe pseudoallylic ($A^{1,3}$) strain exists between *N*-nitroso group and equatorial furfuryl rings at C(2) and C(6). In order to relieve $A^{1,3}$ strain, the *N*-nitroso derivatives **1—3** may adopt alternate chair form or boat form. The possible conformations for the ***E*** isomers of **1—3** are shown in Scheme 1.



Scheme 1. Possible conformations for the ***E***-isomers of **1—3**

The normal chair conformation ***CE*** and boat forms B_4 and B_6 are ruled out since in these conformations $A^{1,3}$ strain exists. The observation of small *vicinal* coupling $J_{H(2),H(3)}$ ruled out the possibility of existing mainly in boat conformations B_2 and B_3 since in these conformations the coupling is expected to be around 10.0 Hz. In the remaining three conformers ***CA***, B_1 and B_5 $J_{2,3}$ is expected to be around 3—4 Hz. In alternate chair form ***CA*** both the *vicinal* couplings $J_{H(5),H(6)}$ and $J_{H(5)',H(6)}$ are expected to be around 3—4 Hz. However in boat forms B_1 and B_5 the couplings are expected to be around 10.0 and 4.0 Hz. The observed coupling constants suggest that these compounds cannot exist in single confor mation. They can exist as an equilibrium mixture of two or three conformers. In boat form B_5, *syn*-1,3-

Table 1

^{1}H *Chemical Shifts* (ppm) *and Coupling Constants* (Hz) *of* **1—8**

Compound	H(2)	H(3)	H(5)	H(6)	Alkyl protons	Aromatic protons
5	3.80 (d, 10.74)	2.81–2.88 (m)	2.81–2.88 (ax) 2.72 (eq) (dd, 3.44, 13.67)	4.17 (dd, 11.72, 3.42)	0.92 (d, 6.34)	6.22 H(3′) & H(3″) 6.29–6.34 H(4′) & H(4″) 7.35–7.39 H(5′) & H(5″)
6	3.92 (d, 11.23)	2.69–2.75 (m)	2.84 (ax) (dd, 3.42, 13.67) 2.69–2.75 (eq) (m)	4.16 (dd, 3.42, 11.72)	0.80 (t, 7.32, $CH_2C\mathbf{H_3}$) 1.28, 1.59 (m, $C\mathbf{H_2}CH_3$)	6.21–6.22 H(3′) & H(3′) 6.29–6.34 H(4′) & H(4″) 7.36–7.39 H(5′) & H(5″)
7	4.19 (d, 11.76)	2.79–2.85 (m)	2.79–2.85 (ax) (m) 2.71 (eq) (dd, 3.44, 14.04)	4.22 (dd, 3.44, 12.09)	0.79 (d, 7.17) 1.05 (d, 7.06) [$CH(C\mathbf{H_3})_2$] 1.97 [$C\mathbf{H}(CH_3)_2$]	6.23–6.36 4(H) 7.29–7.41 2(H)
8	3.75 (d, 10.74)	2.94	2.94	3.75 (d, 10.74)	0.91 (d, 6.83)	6.27 H(3′) & H(3″) 6.32 H(4′) & H(4″) 7.38 H(5′) & H(5″)
1 ***Z***	5.55 (d, 8.22)	3.31–3.24 (m)	3.20–3.11 (m)	6.46 (d, 6.58)	0.97 (d, 6.76)	7.27 (s), 7.19 (s), 7.06 (s), 7.01 (s)
E	5.87 (d, 4.74)	3.31–3.24 (m)	2.94 (dd, 16.87, 4.22) 2.86 (dd, 16.88, 7.52)	6.23 (d, 4.62)	1.17 (d, 7.16)	H(5′) & H(5″) 6.27–6.26, 6.22–6.19 H(4′) & H(4″) 6.08 (s), 5.94 (d), 5.96 (d) H(3′) & H(3″)
2 ***Z***	5.92 (d, 5.24)	2.98 (br. t)	3.23–3.15 (m)	6.48 (d, 6.93)	1.55 (m, $C\mathbf{H_2}CH_3$) 0.91 (t, 7.36, $CH_2C\mathbf{H_3}$)	7.15 (s), 7.04 (s), 7.00 (s) H(5′) & H(5″)
E	5.91 (d, 3.43)	3.09 (br. t)	2.82 (dd, 16.19, 8.22) 2.94 (dd, 16.05, 3.66)	6.43 (dd, 8.09, 3.72)	1.73 (m, $C\mathbf{H_2}CH_3$) 1.02 (t, 7.37, $CH_2C\mathbf{H_3}$)	6.21 (d), 6.16 (d) H(4′) & H(4″) 6.31 (d), 6.10 (d), 6.05 (d) H(3′) & H(3″)
3 ***Z***	5.83 (d, 2.57)	2.78 (d, 8.69)*	2.88 (d, 15.40) 2.75 (dd, 16.43, 9.51)	6.56 (d, 7.86)	1.12 (d, 6.34) 0.92 (d, 6.57) [$CH(C\mathbf{H_3})_2$] 1.94 [m, $C\mathbf{H}(CH_3)_2$]	7.07 (s), 7.05 (s), 6.99 (s), 6.94 (s) H(5′) & H(5″) 6.70 (s), 6.37 (s)
E	5.87 (d, 2.50)	2.57 (d, 10.10)*	3.13 (dd, 15.03, 8.12) 3.05 (d, 14.85)	6.45 (d, 7.71)	1.01 (d, 6.32) 0.85 (d, 6.56) [$CH(C\mathbf{H_3})_2$] 1.68 [m, $C\mathbf{H}(CH_3)_2$]	H(4′) & H(4″) 6.09 (s), 6.05 (s), 5.99 (d) H(3′) & H(3″)
4	*syn* α 5.41 (d, 9.72)	*syn* β 3.35–3.42	*anti* β 3.35–3.42	*anti* α 6.08 (s)	1.02 (d, 6.73) (*syn*) 1.26 (d, 7.29) (*anti*)	7.42 (s), 7.14 (s) H(5′) & H(5″) 6.43–6.41 H(4′) & H(4″) 6.13 (d), 6.23 (t) H(3′) & H(3″)

* $J_{H(3),\,H(7)}$ values.

diaxial interaction exists between furfuryl groups at C(2) and C(6) whereas in boat form $\boldsymbol{B_1}$ such interaction is absent. Therefore the important conformer is $\boldsymbol{B_1}$ only. An equilibrium mixture of boat form $\boldsymbol{B_5}$ and **CA** is ruled out in the present study since in both the forms *syn*-1,3-diaxial interaction is present. Moreover an equilibrium mixture of boat forms $\boldsymbol{B_1}$ and $\boldsymbol{B_5}$ is also excluded in the present study based on the following observations.

The *trans* couplings $J_{H(5),H(6)}$ (*trans*) in the boat forms $\boldsymbol{B_1}$ and $\boldsymbol{B_5}$ are expected to be around 10.0 and 4.0 Hz and the *cis* couplings are expected to be around 4.0 and 10.0 Hz, respectively. An equilib-

Table 2

^{13}C *Chemical shifts* (ppm) *of* **1**—**8**

Compound	C(2)	C(3)	C(4)	C(5)	C(6)	Alkyl carbons	Aromatic carbons
5	60.62	49.51	207.97	46.35	53.97	10.14	153.46, 154.14 C(2′) & C(2″) 141.99, 142.12 C(5′) & C(5″) 110.11, 110.05 C(3′) & C(3″) 107.51, 105.70 C(4′) & C(4″)
6	58.82	56.17	207.63	46.93	54.11	11.78 (CH_2**C**H_3) 18.17 (**C**H_2CH_3)	153.44, 154.16 C(2′) & C(2″) 142.06, 142.17 C(5′) & C(5″) 110.15 C(3′) & C(3″) 107.62, 105.78 C(4′) & C(4″)
7	56.64	59.51	207.24	47.21	53.69	18.05 (**C**H_3) 19.97 (**C**H_3) 26.01 [**C**H$(CH_3)_2$]	154.61, 154.00 C(2′) & C(2″) 141.97 C(5′) & C(5″) 110.27, 110.22 C(3′) & C(3″) 107.51, 105.70 C(4′) & C(4″)
8	61.11	49.60	209.68	49.60	61.11	10.47	153.55 C(2′) = C(2″) 142.07 C(5′) = C(5″) 110.05 C(3′) = C(3″) 107.45 C(4′) = C(4″)
1 ***Z***	52.95	44.42	206.55	40.44	54.99	13.46	150.20, 149.45, 149.39, 148.97 C(2′) & C(2″)
E	60.92	45.39	207.41	38.79	45.65	14.92	143.40, 142.35, 142.09 C(5′) & C(5″) 111.09, 110.77, 110.55, 110.51 C(3′) & C(3″) 109.92, 109.17, 109.09, 108.27 C(4′) & C(4″)
2 ***Z***	48.36	52.06	206.90	39.59	55.41	23.71 (**C**H_2CH_3) 11.68 (CH_2**C**H_3)	149.81, 149.44, 149.34, 148.96 C(2′) & C(2″)
E	59.39	52.81	207.11	38.17	44.41	23.98 (**C**H_2CH_3) 11.49 (CH_2**C**H_3)	143.39, 143.26, 142.47, 142.38 C(5′) & C(5″) 110.87, 110.79, 110.40 C(3′) & C(3″) 109.40, 109.07, 108.80, 108.28 C(4′) & C(4″)
3 ***Z***	45.90	58.26	207.16	39.74	55.83	21.59 (**C**H_3) 20.15 (**C**H_3) 28.73 [**C**H$(CH_3)_2$]	149.71, 149.44, 149.35, 149.02 C(2′) & C(2″) 143.44, 143.09, 142.69, 142.40 C(5′) & C(5″)
E	58.72	58.50	207.06	38.43	43.93	20.80 (**C**H_3) 20.07 (**C**H_3) 28.26 [**C**H$(CH_3)_2$]	110.77, 110.65, 110.35, 110.27 C(3′) & C(3″) 109.52, 108.99, 108.74, 108.22 C(4′) & C(4″)
4	*syn* α 54.65	*syn* β 43.15	208.89	*anti* β 43.49	*anti* α 61.26	12.52 (**C**H_3) (*syn*) 15.77 (**C**H_3) (*anti*)	150.28, 148.78 C(2′) & C(2″) 143.43, 142.03 C(5′) & C(5″) 111.13, 110.64 C(3′) & C(3″) 109.57, 109.44 C(4′) & C(4″)

rium mixture of boat forms $\boldsymbol{B_1}$ and $\boldsymbol{B_5}$ suggests that both couplings are expected to be almost the same and in the region 5—8 Hz. However, the observation of only one coupling around 7.0 Hz (other coupling is of very small magnitude ≈1.0 Hz) in **1**, **3** and two different couplings in **2** (8.09, 3.72 Hz)

ruled out the possibility of existing as an equilibrium mixture of boat forms $\boldsymbol{B_1}$ and $\boldsymbol{B_5}$. Therefore, it is concluded that the ***E*** isomers of *N*-nitroso-3-alkylpiperidin-4-ones **1—3** exist as an equilibrium mixture of boat form $\boldsymbol{B_1}$ and alternate chair form **CA**. Such an equilibrium mixture suggests that one coupling should be small and another coupling should be around 6—8 Hz depending on the population.

In the **Z**-isomers of **2** and **3** small *vicinal* coupling $J_{H(2),H(3)}$ and one large *vicinal* coupling $J_{H(5),H(6)}$ are observed in the ^{1}H NMR spectra. These coupling constants cannot be accounted by normal chair conformation ***CE*** in which severe allylic strain exists. The reverse order of coupling constants in *N*-nitroso-3-methyl derivative **1** [8.22 Hz $J_{H(2),H(3)}$, 6.58 Hz $J_{H(5),H(6)}$] also ruled out the possibility of existing in normal chair conformation ***CE***. Therefore similar to ***E*** isomer, the ***Z*** isomers of **1—3** also exist in conformations other than normal chair form ***CE***. In conformations ***CE***, $\boldsymbol{B_3}$ and $\boldsymbol{B_6}$ allylic strain exists and hence ruled out in the present study.

The conformation $\boldsymbol{B_2}$ is not the major conformer for **2** and **3** since in this conformation $J_{2,3}$ is expected to be around 10.0 Hz which is in contrast to the small couplings observed [5.24 (**2**), 2.57 (**3**) Hz] in **2** and **3**. The boat conformation $\boldsymbol{B_4}$ which avoids $A^{1,3}$ strain can account the observed coupling constants to some extent but molecular mechanics calculations of several *N*-nitroso-*trans*-3-alkyl-*cis*-2,6-diphenylpiperidin-4-ones have shown that the boat form $\boldsymbol{B_4}$ with alkyl groups at flagpole position is having higher energy when compared to alternate chair form ***CA*** and boat forms $\boldsymbol{B_1}$ and $\boldsymbol{B_5}$ [14]. Therefore in the present study, the boat conformation $\boldsymbol{B_4}$ is also excluded. The observation of one large vicinal coupling $J_{H(5),H(6)}$ around 7.0 Hz in **2** and **3** suggest that these compounds cannot exist in single conformation but the major conformer is $\boldsymbol{B_1}$ only.

In alternate chair form ***CA*** both the *vicinal* couplings $J_{H(5),H(6)}$ and $J_{H(5)',H(6)}$ are expected to be around 3—4 Hz. In boat forms $\boldsymbol{B_1}$ and $\boldsymbol{B_5}$ the two couplings are expected to be around 10.0 and 4.0 Hz. An equilibrium mixture of boat forms $\boldsymbol{B_1}$ and $\boldsymbol{B_5}$ for the ***Z*** forms of *N*-nitroso-3-alkylpiperidin-4-ones **2—3** is also ruled out based on the same arguments given for ***E*** form. Therefore, it is concluded that the ***Z*** isomers of **2** and **3** also exist as an equilibrium mixture of boat conformation $\boldsymbol{B_1}$ (major) and alternate chair form ***CA*** (minor) similar to ***E*** isomers.

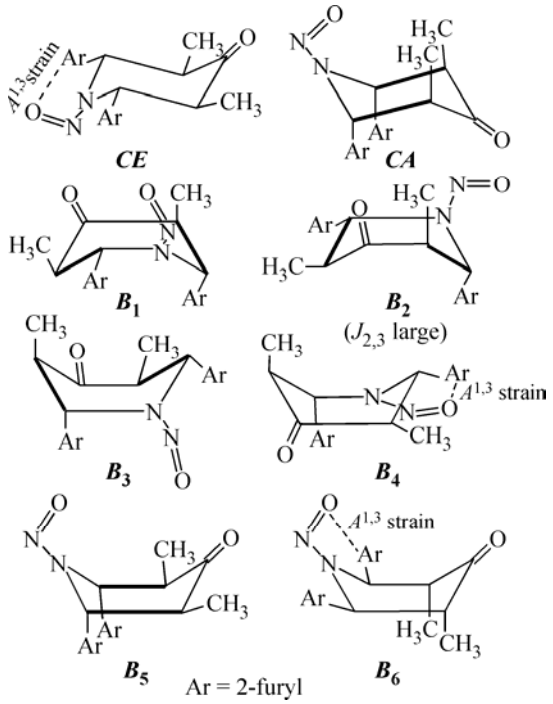
In the ***Z*** isomer of *N*-nitroso-3-methyl derivative **1** large *vicinal* couplings $J_{H(2),H(3)}$ (8.22 Hz) and $J_{H(5),H(6)}$ (6.58 Hz) are observed which is in contrast to the values observed in the corresponding ***E*** isomer. These large couplings ruled out the possibility of existing in alternate chair form ***CA***. In conformations ***CE***, $\boldsymbol{B_3}$ and $\boldsymbol{B_6}$ allylic strain exists and hence ruled out in the present study. The observation of large coupling $J_{H(2),H(3)}$ suggests that the major conformer is $\boldsymbol{B_2}$ in which $A^{1,3}$ strain is avoided. A significant amount of boat form $\boldsymbol{B_1}$ is also present in solution in addition to $\boldsymbol{B_2}$ for the **Z** isomer of *N*-nitroso-3-methyl derivative **1**.

The population of the alternate chair form ***CA***/boat form **1—3** can be predicted using the following relation for all the compounds except **1*Z*** $J_{5,6}(\text{obs}) = xJ_{5,6}(\boldsymbol{CA}) + (1 - x)J_{5,6}(\boldsymbol{B_1})$ where $J_{5,6}(\boldsymbol{B_1})$ and $J_{5,6}(\boldsymbol{CA})$ are the *trans* couplings expected in the boat form $\boldsymbol{B_1}$ and alternate chair form ***CA*** and the values are taken to be 10.0 and 4.0 Hz, respectively, and x is the contribution of alternate chair form present in the equilibrium. For **1*Z***, a similar equation can be written involving the coupling $J_{5,6}(\boldsymbol{B_2})$ $J_{5,6}(\text{obs}) = xJ_{5,6}(\boldsymbol{B_1}) + (1 - x)J_{5,6}(\boldsymbol{B_2})$ where $J_{5,6}(\boldsymbol{B_1})$ and $J_{5,6}(\boldsymbol{B_2})$ are the *trans* couplings expected in the boat form $\boldsymbol{B_1}$ and $\boldsymbol{B_2}$ and the values are taken to be 10.0 and 4.0 Hz, respectively, and x is the contribution of $\boldsymbol{B_1}$ present in the equilibrium. The populations of the various forms calculated in this manner are as follows.

Compound	***CA***	$\boldsymbol{B_1}$	$\boldsymbol{B_2}$	Compound	***CA***	$\boldsymbol{B_1}$	$\boldsymbol{B_2}$
1*E*	89.7	10.3	—	**1*Z***	—	43.0	57.0
2*E*	31.8	68.2	—	**2*Z***	51.2	48.8	—
3*E*	38.2	61.8	—	**3*Z***	35.7	64.3	—

***N*-Nitroso-*t*(3),*t*(5)-dimethyl-*r*(2),*c*(6)-bis(2′-furyl)piperidin-4-one 4.** Comparison of coupling constants about *syn* α-*syn* β bond and *anti* α-*anti* β bond in *N*-nitroso-3,5-dimethylpiperidin-4-one **4** with those of the corresponding parent 3,5-dimethylpieridin-4-one **8** reveals that there is a drastic change in the coupling constants due to *N*-nitrosation. This ruled out the possibility of ex-

isting in normal chair conformation ***CE*** with equatorial orientations of all the substituents. The possible conformations for *N*-nitroso-3,5-dimethylpiperidin-4-one **4** are shown in the Scheme 2. Boat conformations $\boldsymbol{B_1}$ and $\boldsymbol{B_2}$ are equivalent and they differ in the orientation of nitroso group only. Similarly boat conformations $\boldsymbol{B_3}$ and $\boldsymbol{B_4}$ differ in the orientation of nitroso group only.



Scheme 2. Possible conformation of **4**

The observation of large coupling about *syn* α-*syn* β bond (9.72 Hz) and singlet for *anti* α proton in **4** ruled out the possibility of existing in boat conformations $\boldsymbol{B_5}$ and $\boldsymbol{B_6}$ since in these conformations on both sides small coupling (~4.0 Hz) is expected. In alternate chair form ***CA*** severe *syn* 1,3-diaxial interaction exists between furfuryl groups at C(2) and C(6) and also between CH_3 groups at C(3) and C(5) and hence not favoured.

The boat conformations $\boldsymbol{B_3}$ and $\boldsymbol{B_4}$ are of higher energy compared to boat form $\boldsymbol{B_1}$ and $\boldsymbol{B_2}$ since methyl group is in the flagpole position and hence not favoured. Therefore, the favoured conformation may be $\boldsymbol{B_1}$ or $\boldsymbol{B_2}$. In boat form $\boldsymbol{B_1}$ *syn* α proton is expected to be associated with large coupling (~10.0 Hz). However in boat form $\boldsymbol{B_2}$, the *syn* α proton should be associated with small coupling (~4.0 Hz) .The *syn* α proton (5.41 ppm) is actually associated with large coupling (9.72 Hz) compared to *anti* α proton (6.08 ppm singlet; coupling is very small). Thus, the favoured conformation for the *N*-nitroso-3,5-dimethyl derivative **4** is the boat conformation $\boldsymbol{B_1}$; only this conformation is further supported by the X-ray studies reported previously [24].

Conformation of isopropyl group at C(3) in 3. The possible conformations of isopropyl group at C(3) in the boat conformation $\boldsymbol{B_1}$ of *N*-nitroso-3-isopropyl derivative **3** are shown in Fig. 3. In conformations **A** and **C** only small coupling around 4 Hz is expected for $J_{H(3),H(7)}$. The observed large $J_{H(3),H(7)}$ value [8.69 Hz (***Z***); 10.10 Hz (***E***)] supports that H(3) should be *anti* to H(7) and hence predicts conformation ***B*** for **3** 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.

Semiempirical molecular orbital calculation. The molecular structures of the *N*-nitrosoamines **1**—**4** were calculated using AM1 Hamiltonian available in Argus lab [28, 29] (version 4.0) on a Pentium personal computer. Table 3 shows the relative heats of formation of the various conformers corresponding to the calculated energy minimum. For *N*-nitroso-3,5-dimethyl derivative **4**

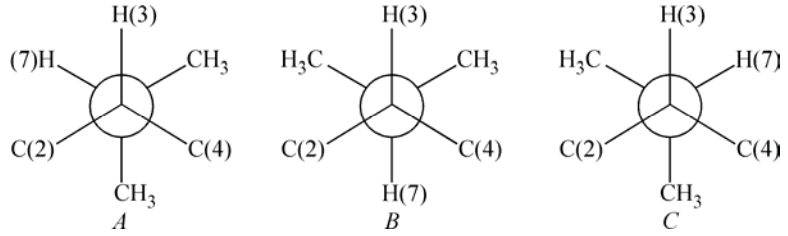


Fig. 3. Possible conformations of isopropyl group at C(3) in **3**

T a b l e 3

Calculated Relative Formation Energies (kJ/mol) *of Various Conformers of N-nitrosopiperidines* **1—4**

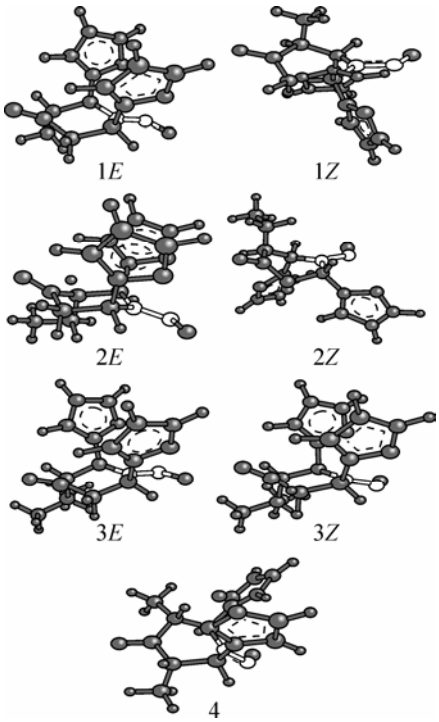
Compound	***CE***	***CA***	B_1	B_2	B_3	B_4	B_5	B_6
1*Z*	10.99	2.59	0	6.94	8.90	0.54	17.97	8.36
2*Z*	13.42	2.93	0	7.40	14.50	1.00	0.17	13.67
3*Z*	1.42	0	0.42	12.62	12.66	1.00	1.38	11.07
1*E*	6.98	0	2.80	1.84	0.59	4.14	13.84	4.60
2*E*	9.11	0	2.51	0.84	5.35	4.09	1.80	9.57
3*E*	6.06	0	5.31	8.69	9.11	9.15	9.78	9.78
4	9.15	0.71	0	8.28	2.80	4.51	6.77	17.01

theoretical study predicts B_1 as the minimum energy conformer which is further supported by coupling constant data. The theoretical calculation reveals ***CA*** as the minimum energy conformer and B_1 as the next significant conformer (minor) for both the ***E*** and ***Z*** isomers of *N*-nitroso-3-isopropyl derivative **3**. The coupling constants also predict an equilibrium mixture of alternate chair form ***CA*** and boat form B_1 but with reverse population ratio ~ ***CA*** (35—38 %) and B_1 (62—65 %). However both the analyses are in agreement with the fact that the alternate chair form (***CA***) and boat form (B_1) are the two significant conformers present in the equilibrium in **3**.

For the ***E*** isomer of *N*-nitroso-3-methyl derivative **1** both the theoretical study and coupling constants predict ***CA*** as the major conformer. However in **1*Z*** theoretical studies predict the boat form B_1 as the major conformer but coupling constants predict that it should be the minor form (~43 %). Similarly in **2*Z*** coupling constants predict roughly equal population of boat form B_1 and alternate chair form ***CA*** and theoretical study predicts B_1 as the (major isomer) minimum energy conformer. However in **2*E*** theoretical study predicts ***CA*** as the major conformer but it is the minor isomer according to the coupling constant data. Thus, the presence of one conformer in the equilibrium can be predicted to a reasonable accuracy by both theoretical studies and coupling constant data in **1** and **2**. Regarding another significant conformer present in equilibrium in **1** and **2**, there is a discrepancy between the results derived from theoretical and coupling constant studies. The optimized structures corresponding to the stable conformers of **1—4** are shown in Fig. 4.

To predict the favoured conformation of isopropyl group at C(3) in **3**, theoretical calculations were also performed for the three possible conformations shown in Fig. 3. The relative heats of formation for the conformers are 2.05 (**A**), 0.0 (***B***) and 1.78 (**C**) kcal/mol for the ***E*** isomer and 2.01 (**A**), 0.0 (***B***) and 1.83 (**C**) kcal/mol for the ***Z*** isomer. Both the theoretical study and coupling constants show that for **3*Z*** and **3*E*** the favoured conformation of isopropyl group is the one in which H(3) and H(7) are *anti* to each other, *i.e*. conformation ***B***.

Analysis of chemical shifts. In normal chair conformation it is seen that the *anti* α protons (*anti* to N—N=O bond) are deshielded to an extent of ~1.11 ppm (axial) and ~1.60 ppm (equatorial) and the *syn* equatorial α protons are deshielded to an extent of ~1.94 ppm due to *N*-nitrosation [30—32]. There is slight shielding (~ –0.26 ppm) on the *syn* α axial proton if equatorial hydrogen is attached to *syn* α carbon.



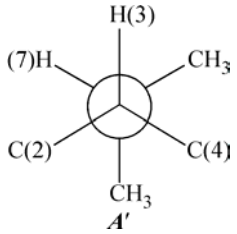


Fig. 4 (*left*). Optimized structure of stable conformers of *N*-nitroso derivatives **1—4**

Fig. 5 (*right*). Favoured conformation of isopropyl group in **7**

Comparison of the chemical shifts of *N*-nitroso derivatives **1—4** with those of the corresponding parent piperidin-4-ones **5—8** reveal that the replacement of —NH by —N—N=O group deshields most of the heterocyclic ring protons and alkyl protons at C(3) and the observed deshielding magnitudes are displayed in Table 4. 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 +1.64 to 2.29 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 in the normal chair conformation ***CE***. Moreover, the deshielding magnitude observed on *anti* α protons [H(2) in the ***E*** isomer; H(6) in the ***Z*** isomer] is also higher [+1.68 to 2.34 ppm] 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 conformations in which *syn* α protons lie in the same plane of the N—N=O moiety.

It is very surprising to note that H(3) proton is shielded whereas H(5) proton is deshielded due to *N*-nitrosation in **3**. The shielding observed on H(3) due to *N*-nitrosation is probably due to the different conformations of the isopropyl group in the parent piperidin-4-one **5** and its *N*-nitroso derivative **3**. In the chair conformation of the parent isopropylpiperidin-4-one **7**, it has been previously established [24] that among the three possible conformations for isopropyl group the favoured conformation of isopropyl group at C(3) is ***A′*** (Fig. 5) in which H(3) is *gauche* to one methyl group and *anti* to the other methyl group and hence experiences shielding due to magnetic anisotropic effect of *gauche* methyl group of isopropyl moiety alone. In the favoured conformation ***B*** for the *N*-nitroso derivative **3**, H(3) proton experiences shielding due to magnetic anisotropic effect of both the methyl groups and this is the probable reason for the shielding observed on H(3) in **3** due to *N*-nitrosation. *N*-Nitrosation shields *syn* α carbons by ~7.50 ppm but deshields *anti* α carbons by ~4.0 ppm in normal chair conformation ***CE*** [33—35]. It is seen from the Table 2 that *N*-nitrosation shields all the heterocyclic ring carbons except C(2) in the ***E*** isomers of **1—3** and C(6) in the ***Z*** isomers of **1—3**. The shielding and deshielding magnitude observed on ring and alkyl carbons due to *N*-nitrosation in **1—4** are also displayed in Table 5.

Table 5 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 deshielding observed on *anti* α carbons [C(2) in ***E*** isomer and C(6) in the

Table 4

Observed ^{1}H *Deshielding Magnitude* (ppm)* *in N-Nitrosopiperidin-4-ones* **1—4**

Compound	H(2)	H(3)	H(5)	H(6)	Alkyl
1*Z*	+1.75	+(0.50–0.36)	+(0.39–0.23) +(0.48–0.39)	+2.29	+0.05
1*E*	+2.07	+(0.50–0.36)	(–0.02 to +0.05) (0.22)	+2.06	+0.25
2*Z*	+2.00	+(0.29–0.23)	+(0.39–0.31) +(0.54–0.40)	+2.32	+0.27 (C**H**$_2$CH$_3$) +0.11(C**H**$_3$)
2*E*	+1.99	+(0.40–0.34)	(–0.02) +(0.25–0.19)	+2.27	+0.45 (C**H**$_2$CH$_3$) +0.22 (C**H**$_3$)
3*Z*	+1.64	–0.01 to –0.07	–0.04 to –0.10 + 0.17	+2.34	–0.03 [C**H**(CH$_3$)$_2$] + 0.07, +0.13 [CH(**CH**$_3$)$_2$]
3*E*	+1.68	–0.22 to –0.28	+ (0.34–0.28) + 0.34	+2.23	–0.29 [C**H**(CH$_3$)$_2$] –0.04, + 0.06 [CH(**CH**$_3$)$_2$]
4	*syn* α +1.66	*syn* β +(0.41–0.48)	*anti* β +(0.41–0.48)	*anti* α +2.33	+0.11 +0.35

* Calculated relative to compounds **5—8**.

Table 5

Observed ^{13}C *Shielding and Deshielding Magnitude* (ppm)* *in N-nitrosopiperidin-4-ones* **1—4**

Compound	C(2)	C(3)	C(4)	C(5)	C(6)	Alkyl carbons
1*Z*	–7.67	–5.09	–1.42	–5.91	+1.02	+3.32
1*E*	+0.30	–4.12	–0.56	–7.56	–8.32	+4.78
2*Z*	–10.46	–4.11	–0.73	–7.34	+1.30	+5.54 (**C**H$_2$CH$_3$) –0.10 (CH$_2$**C**H$_3$)
2*E*	+0.57	–3.36	–0.52	–8.76	–9.70	+5.81 (**C**H$_2$CH$_3$) –0.29 (CH$_2$**C**H$_3$)
3*Z*	–10.74	–1.25	–0.08	–7.47	+2.14	+2.72 [**C**H(CH$_3$)$_2$] +1.62 (**C**H$_3$) +2.10 (**C**H$_3$)
3*E*	+2.08	–1.01	–0.18	–8.78	–9.76	+2.25 [**C**H(CH$_3$)$_2$] +0.83 (**C**H$_3$) +2.02 (**C**H$_3$)
4	*syn* α –6.46	*syn* β –6.45	–0.79	*anti* β –6.11	*anti* α +0.15	+2.05 (**C**H$_3$) +5.30 (**C**H$_3$)

* Calculated relative to compounds **5—8**.

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 configuration of alkyl groups at C(3) in **1—4** compared to the corresponding parent piperidin-4-ones **5—8**. All these values support other than normal chair conformation for **1—4**, *i.e.* conformation in which *syn* α hydrogens lie in the same plane of N—NO moiety.

CONCLUSIONS

The conformations of ***E*** and ***Z*** isomers of *N*-nitroso-*t*(3)-alkyl-*r*(2),*c*(6)-bis-(2′-furyl)piperidin-4-ones **1—3** [alkyl = CH$_3$, C$_2$H$_5$ and CH(CH$_3$)$_2$] except **1*Z*** are established to be an equilibrium mixture of boat form $\boldsymbol{B_1}$ and alternate chair form ***CA*** by ^{1}H and ^{13}C spectral studies. The conformation of **1*Z*** is predicted to be an equilibrium mixture of the boat forms $\boldsymbol{B_2}$ and $\boldsymbol{B_1}$ and the *N*-nitroso-*t*(3),*t*(5)-dimethyl-*r*(2),*c*(6)-bis(2′-furyl)piperidin-4-one **4** exists in boat conformation $\boldsymbol{B_1}$ only. Semiempirical calculations also support the conformations in **3—4**. The presence of one conformer in the equilibrium can be predicted to a reasonable accuracy by theoretical studies in **1—2**. *N*-Nitrosation deshields α-

and β-protons but shields α- and β-carbons and the deshielding/shielding magnitude are also in line with these conformations.

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