INTRODUCTION
1. Introduction

1.1 Conformational Analysis of Simple Heterocycles

Extensive stereochemical investigations have been made on the conformationally anchored piperidine rings such as 2,6-diarylpiperidin-4-ones (1a-e) employing principally $^1H$, $^{13}C$ and $^{17}O$ NMR analysis and kinetic methods.1-3

The piperidine ring in these compounds is anchored by incorporating two aryl groups at α-positions in cis-relationship. The alkyl and aryl substituents at C(3) and C(5) were found to occupy equatorial orientations.4-6 The NMR analysis of cis-2,6-diphenylpiperidines (2-6) showed that on increasing the bulkiness of the substituent at C(3), the degree of flattening also increased.7

Reductions of the heterocyclohexanones (7a-c) resulted in the formation of a pair of cis and trans alcohols. The configurations of a few 4-heterocyclohexanols have been assigned on the basis of $^{13}C$ chemical shift data. An upfield shift of about 5.0 ppm was noted for an axial hydroxyl bearing carbon. The C(2,6) and C(3,5) carbons were also shielded approximately by 5.0 and 3.0 ppm, respectively, in the trans isomer (axial OH).3 For example, the hydroxyl group of cis-2,6-diphenylpiperidin-trans-4-ol (8a, β-isomer) shielded the C(4) carbon by 5.4 ppm more than that for the C(4) carbon of the α-isomer 8b (Scheme 1).3
1 a) $\text{Ar} = \text{Phenyl}$  
b) $\text{Ar} = \text{o-Chlorophenyl}$  
c) $\text{Ar} = \text{p-Chlorophenyl}$  
d) $\text{Ar} = \text{p-Nitrophenyl}$  
e) $\text{Ar} = \text{p-Tolyl etc}$

2 $R, R^1 = H$

3 $R = \text{Me}, R^1 = H$

4 $R = \text{Et}, R^1 = H$

5 $R = \text{I-Pr}, R^1 = H$

6 $R, R^1 = \text{Me}$

7 a) $X = S$  
b) $X = \text{NCH}_3$  
c) $X = \text{NH}$
SCHEME 1
H
X=CO

9

X=CO

10
1.2 Conformational Preferences of Bicyclic Compounds

Bicyclo[3.3.1]nonanes with simple substituents preferred to adopt chair-chair conformations with slight ring flattening^\textsuperscript{8a-c} while those with bulky substituents at 3 or 7 endo positions preferred chair-boat conformations.\textsuperscript{8d,e} The cis-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one (9)^\textsuperscript{8f,g} was found to exist in chair-chair conformation in the solid state as well as in solution.\textsuperscript{8} The configurations and conformations of several 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ols, 2,4-diaryl-7-hetera-3-azabicyclo[3.3.1]nonan-9-ols were analysed by \textsuperscript{13}C NMR spectroscopy on the basis of the gamma-gauche effect\textsuperscript{9} due to hydroxyl group. The introduction of a hydroxyl group at C(9) of 9 did not alter the chemical shift of C(7) indicating that compound 9 preferred twin-chair conformation with syn or anti orientations of the hydroxyl group. The hydroxyl group was considered to be axial to the cyclohexane ring when the C(6,8) were shifted upfield, and equatorial when C(2,4) carbons were upfield shifted.\textsuperscript{10}

A few 2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]nonane (10) have also been analysed by making use of \textsuperscript{1}H NMR and \textsuperscript{13}C NMR and X-ray studies.\textsuperscript{11} The diazabicyclic compounds preferred chair-boat conformation with all the aryl groups in the equatorial orientations.
FIGURE 1

a) $R, R' = H$

b) $R, R' = Me$

c) $R, R' = Et$

d) $R, R' = i-Pr$
1.3 Conformation of the Five-membered Ring Systems

The five-membered ring has been found to preferentially exist in a puckered conformation.\textsuperscript{12} There are two puckered forms for cyclopentane, the C\textsubscript{2} or half-chair form A and C\textsubscript{g} or envelope form B (Fig 1).\textsuperscript{13} In monosubstituted cyclopentanes, the envelope form was favoured with the substituent in the pseudo-equatorial position of the flap carbon. In this conformation, the eclipsing interaction between the substituent and the hydrogens on the adjacent carbon atoms are relieved.

1.3.1 Conformational Preference of 1,3-Oxathiolanes

The assignments of chemical shifts of the 2-t\textsubscript{-}butyl-1,3-oxathiolane (11) have been made employing the observation that the equatorial hydrogen on cyclohexyl systems appeared at lower fields than the axial counterparts.\textsuperscript{14} The dihedral angles and the coupling constants (J\textsubscript{1,3} and J\textsubscript{2,4}) of t\textsubscript{-}butyl-1,3-oxathiolane (11) and 2,2-disubstituted oxathiolanes 12 were in agreement with the distorted envelope conformation with oxygen as the 'flap atom'.\textsuperscript{15}

1.3.2 Stereochemistry of Spiro-Oxathiolanes

Eliel et al. treated t\textsubscript{-}butylcyclohexanone (13) with 2-mercaptoethanol in the presence of acid and isolated a mixture of diastereoisomeric monothioketals 14 and 15 in 74\% yield along with 4\% of the parent ketone.\textsuperscript{16}
$X = S, O$

16
The assignment of configuration of the isomeric 4-t-butylcyclohexane monothioketals 14 and 15 was made on the basis of the chemical shifts of protons in the $^1$H NMR spectra of 4-t-butylcyclohexylmethyl ether (16). The equatorial methoxy group/thiomethyl group in 16 appeared at lower field region (δ 3.25 & 2.0 ppm) when compared to the axial groups (δ 3.21 & 1.98 ppm). Therefore the OCH$_2$ and SCH$_2$ protons of monothioketals 14 and 15 which appeared at lower field corresponded to the equatorial groups. It was inferred that the isomer 15 with lower field SCH$_2$ chemical shift had the equatorial sulfur and axial oxygen whereas the isomer 14 had the axial sulfur and equatorial oxygen.

The configuration of the stereoisomeric 4-t-butylcyclohexane monothioketals has been further confirmed through oxidation rate data of the corresponding sulfoxides with perbenzoic acid. The presumed equatorial sulfoxide reacted about twice as much fast as the axial. Definite assignment by oxidation rate studies failed in this case as the appropriate sulfoxides could not be isolated. The oxidation rate supported the previous assignment of configuration by Eliel et al., since on steric grounds the axial sulfoxide function should certainly be more hindered and therefore less easily attacked than the equatorial sulfoxide function. In order to give an explanation for the assigned configuration of the stable isomer, leverage effect was suggested. The geometry of the five-membered ring required
the axial substituent to bend outward, away from the syn-axial hydrogen atom in the cyclohexane ring. For a given angle deformation, the bending outward relieved the compression of the sulfur atom with the syn-axial hydrogen more than that of the oxygen since the C-S bond is longer than that of C-O bond and hence the sulfur atom moved through a larger distance.\textsuperscript{17a} Allinger et al.\textsuperscript{17b} have suggested an explanation for the leveling effect in a number of 1,1-disubstituted cyclohexan-
one.

The configuration of \textit{t}-butylcyclohexane monothioketals 14 and 15 was confirmed on the basis of gamma-gauche effect.\textsuperscript{18} It was found that the upfield shift of C(3,5) carbons of the isomer 14 relative to those of the \textit{t}-butylcyclohexane 17 was 1.60 ppm and the second isomer 15 2.85 ppm. Since the oxygen atom is more electronegative than that of sulfur atom, the one having higher upfield shift was considered as the isomer with oxygen axial to the ring.\textsuperscript{18}

The configuration of 3-azabicyclo[3.3.1]nonane monothio-
ketal 18 at C(9) was assigned by comparing the chemical shifts at C(6,8) with those of the diastereomeric 4-\textit{t}-butyl-
cyclohexane monothioketals 14 and 15. The upfield shift of C(6,8) carbons in compound 18 relative to the corresponding carbons in 3-azabicyclo[3.3.1]nonane (19) was 0.36 ppm which indicated a configuration involving sulfur axial to the cyclohexane ring and that of C(2,4) was 5.35 ppm in agreement with oxygen axial to the piperidine ring.\textsuperscript{19}
The 9-methylene-7-oxa-1-thiaspiro[4.5]decan-8-one (20) and cis-8-t-butyl-3-methylene-1-oxaspiro[4.5]decan-2-one (21), synthesised via Reformatsky type reaction on the substituted 4-thianones and t-butylcyclohexanone, were characterised by $^1$H, $^{13}$C NMR as well as by mass and IR spectra. Only one isomer has been isolated in each case. The configuration at C(4) of 20 has been assigned to be C-O bond axial to the ring. Upfield shifts of 4.46 and 3.79 ppm for C(2) and C(6) carbons in compound 20 were found in comparison with parent thianes due to the gamma-gauche effect of the axial C-O bond. Similar upfield shifts for C(7,9) were also observed in the case of 21 in comparison with the parent t-butylcyclohexane (17).

1.4 Stereochemistry of N-Nitroso- and N-Acylpiperidines and N-Nitrosoazabicyclo[3.3.1]nonanes

Due to the interesting stereochemistry, biological importance and synthetic utility, the stereochemistry of a number of N-substituted cis-2,6-diarylpiperidines has been studied in our laboratory.

Lunazzi et al., have studied the stereochemistry of N-nitroso, N-acyl and N-imino derivatives of cis-2,6-dimethylpiperidine and 2,2',6,6'-tetramethylpiperidine. The presence of partial N-N double bond character in nitrosamines (due to extensive delocalization of the lone pair of electrons on the nitrogen with the hetero pi-electron system) caused two
SCHEME 2

HONO

22
Figure 2 Allylic strain and the conformational preference of alpha methyl groups
23-\(X=Y\) is

- a  COCH\(_3\)
- b  COPh
- c  COCH\(_2\)Ph

24-\(X=Y\) is

- a  CHO
- b  COCH\(_3\)
- c  COPh
- d  COCH\(_2\)Ph
- e  SO\(_2\)CH\(_3\)
- f  SO\(_2\)C\(_6\)H\(_4\)CH\(_3\)
- g  NO

\[23-\text{X}=\text{Y} = \text{COCH}_3\]
\[24-\text{X}=\text{Y} = \text{CHO}\]

**FIGURE 3**

**FIGURE 4**
different methyl signals in the $^1$H NMR spectrum of dimethylnitrosamine (22). The methyl groups in $\text{N-}$nitroso-cis-2,6-dimethylpiperidine preferentially occupied axial positions, the reason being $A^{1,3}$-strain (Scheme 2). In general, $A^{1,3}$-strain, proposed by Johnson, is considered to be a severe nonbonded interaction between the group $'X=Y'$ bearing $\pi$-electrons and an alkyl group present at allylic position of a cyclic system (Fig. 2). Chow et al. studied the stereochemistry of a series of N-nitroso and N-acyl derivatives of 2-methylpiperidines (23a-c) and cis-2,6-dimethylpiperidines (24a-g). The resonance energy for N-N-O delocalization was determined to be 63-84 kJ/mole while the 1,3-diaxial CH$_3$/CH$_3$ interaction was only 14.6 kJ/mole. The gain in stabilization energy was about 50-71 kJ/mole in the diaxial conformer. In all these cases, the alkyl groups were forced to occupy preferentially axial positions due to $A^{1,3}$-strain.

The double bond character in amides arises due to the delocalization of lone pair of electrons on nitrogen with the carbonyl $\pi$-electrons. In $\text{N,N-}$dimethylformamide (Fig 3), the protons of the N-methyl group cis to oxygen resonated at higher field than those trans to oxygen and the cis-methyl protons experienced the greater shielding. This observation was explained with the model proposed by Paulsen and Todt. In the model (Fig. 4), there are two regions, the "in-plane" region (deshielded region) in the plane of the amide group...
FIGURE 5

FIGURE 6
with positions aa' and dd' in which "a" experienced greater shielding than "a'" and the "out-of-plane region" (shielded region) in which the c and c' positions are opposed, the position c' being shielded than c.

Aromatic Solvent Induced Shift Study (ASIS)

The syn and anti benzylic protons with reference to the nitroso oxygen in nitrosopiperidines (Fig. 5) were assigned making use of "Aromatic Solvent Induced shifts" (ASIS)\textsuperscript{42} and HETCOR\textsuperscript{29,30} studies. In ASIS study, the signals due to the α-protons which are syn or anti to the oxygen atom of the nitroso group were differentiated by comparing the $^1$H NMR spectra recorded in deutrated benzene and chloroform. The basic principle of the ASIS study is that the aromatic solvent molecules preferred to arrange in a manner that the protons which are anti to the oxygen atom of the nitroso group are more shielded than the protons which are syn to the nitroso group due to the repulsion between both the electron pairs of the oxygen atom of the nitroso group and the p-π electron of the aromatic ring. The above explanation was based on the charge transfer complex formed between the nitrosamine and benzene (Fig. 6). Due to the repulsion between the lone pair of electrons on oxygen of the nitroso group and aromatic π-cloud, the association of the benzene molecules with the syn protons was restricted compared to the anti protons.
25

26 X=CO; R,R'=H
27 X=CO; R=Me, R'=H
28 X=CO; R=Et, R'=H
29 X=CO; R=i-Pr, R'=H
30 X=CO; R,R'=Me
31 X=CO; R,R'=Ph
32 X=CH₂; R,R'=H
33 X=CH₂; R=Me, R'=H
34 X=CH₂; R=i-Pr, R'=H
35 X=CH₂; R,R'=Me
$^1\text{H}-^{13}\text{C}$ Correlation Spectroscopy (HETCOR)

The $N$-nitroso compounds such as $N$-nitroso-2,7-diphenyl-hexahydrodiazepin-5-one (25)\(^\text{30}\) and $N$-nitroso-2,3,5,6-tetraphenylpiperidin-4-one (31)\(^\text{29}\) studied in our laboratory showed downfield shifts for both the syn and anti proton signals. Hence for the assignment of syn and anti proton signals $^1\text{H}-^{13}\text{C}$ correlation ($^1\text{H}-^{13}\text{C}$ HETCOR) spectroscopy was used. The assignments were based on the generalization\(^\text{43}\) that in compounds containing $N$-$X=Y$ systems, the signal corresponding to the alpha carbon syn to $-X=Y$ functions appears upfield due to gamma-eclipsing interaction compared to that anti to $-X=Y$ group. The cross peaks correlating syn and anti carbon signals were directly assigned to the signals of syn and anti protons, respectively, by $^1\text{H}-^{13}\text{C}$ HETCOR spectrum.

1.4.1 Conformational Preference of $N$-Nitrosopiperidines (26-35)

The $N$-nitrosopiperidin-4-ones 26-31 and $N$-nitrosopiperidines 32-35 were found to prefer twist-chair conformations with pseudo-axial orientations of the alpha substituents.\(^\text{29,31a}\) The nitroso group was found to be coplanar in all the nitroso compounds. The observation of two different carbon signals in the $^{13}\text{C}$ NMR spectra was attributed to the syn and anti orientations of the $N$-$N$-$O$ group.

Unlike the dialkyl-$N$-nitrosopiperidines which preferred a conformation with diaxial alkyl groups, the diaryl-$N$-
FIGURE 7 Crystal Structure of ε-3-isopropyl-ε-2,ε-6-diphenylpiperidin-4-one.
**Figure 8** Crystal Structure of \( r-2, t-3, t-5, g-6-\)tetraphenylpiperidin-4-one.

\[
\begin{align*}
36 \quad Ar &= \begin{array}{c}
\text{c} \\
\text{b} \\
\text{a}
\end{array} \\
&= \begin{array}{c}
\text{C} \\
\text{N} \\
\text{O}
\end{array} \\
&= \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array} \\
&= \begin{array}{c}
R_1 \\
R_2
\end{array}
\end{align*}
\]
nitrosopiperidines 32–35 preferred a conformation with diequatorial phenyl groups even though the nitroso group is coplanar to the dynamically averaged plane of the piperidine ring.

The low coupling constant (0.3 Hz) for one of the doublets of the benzylic protons of 3-isopropyl-N-nitroso-2,6-diphenylpiperidin-4-one (29) indicated the flattening at C(2)-N(1)-C(6) portion of the ring and the partial flattening around C(3) atom due to the bulkiness of the isopropyl group at C(3). Interestingly, the X-ray studies on 3-isopropyl-N-nitroso-2,6-diphenylpiperidin-4-one (29) showed that the N-nitroso compound 29 adopted a chair conformation in which all the ring substituents occupied axial orientations (Fig. 7). The torsional angles C7-C2-C3-C13: 162.9°, C6-N1-C2-H2: 171.9° and H3-C3-C4-C5: 171.4° indicated the axial orientation of the three substituents. The $\text{A}^{1,3}$-strain might have forced the ring to flip to the alternate chair conformation. The N-nitroso-2,3,5,6-tetraphenylpiperidin-4-one (31) was found to prefer sofa conformation with pseudo-equatorially oriented alpha substituents (Fig. 8).

1.4.2 Stereodynamics of N-Nitroso, N-Formyl and N-Acetyl-2,6-
diheteroarylpiperidin-4-ones (36–38)

The influence of lone pair-lone pair repulsions (between the hetero atoms (O,S,Cl) of the alpha substituents and the nitroso/acyl oxygen) and the steric strain between 1,3-diaxial
a. \( \text{Ar} = \text{Ph}; R_1 = R_2 = R_3 = H \)

b. \( \text{Ar} = \text{Ph}; R_1 = \text{Me}; R_2 = R_3 = H \)

c. \( \text{Ar} = \text{Ph}; R_1 = \text{Et}; R_2 = R_3 = H \)

d. \( \text{Ar} = \text{Ph}; R_1 = \text{iPr}; R_2 = R_3 = H \)

e. \( \text{Ar} = \text{Ph}; R_1 = H; R_2 = R_3 = \text{Me} \)

f. \( \text{Ar} = \text{Ph}; R_1 = R_2 = \text{Me}; R_3 = H \)

g. \( \text{Ar} = \text{2-thienyl}; \ R_1 = R_2 = R_3 = H \)

h. \( \text{Ar} = \text{o-chlorophenyl}; \ R_1 = R_2 = \text{Me}; R_3 = H \)

i. \( \text{Ar} = \text{o-anisyl}; \ R_1 = R_2 = \text{Me}; R_3 = H \)  

\( X = \text{CH}_2 \)  

j. \( \text{Ar} = \text{Ph}; \ R_1 = R_2 = R_3 = H \)
or 1,3-diequatorial heteroaryl groups on the conformational preferences of the N-nitroso and N-acyl piperidin-4-ones were examined.\textsuperscript{33} The nitroso and the acyl groups were found to be coplanar. In the case of N-nitroso-2,6-diheteroarylpiperidin-4-ones (36a-c), the coupling constants were 9.5±0.5 Hz for one of the doublets (δ 5.3±0.2 ppm) and 3.5±0.5 Hz for the other doublet (δ 6.3±0.2 ppm). But in the corresponding parent piperidin-4-ones, a doublet (δ 3.5±0.5 ppm) for benzylic protons (H2 and H6) with a vicinal coupling constant of 10.5±0.2 Hz was observed. The unequal vicinal coupling constants and dihedral angles showed that the N-nitrosopiperidin-4-ones preferred twist-boat conformations. Due to the N-N/N-C restricted rotation, the N-nitroso/N-acyl compounds were found to be in equilibrium between two rotamers. The crystal structure of N-nitroso-2,6-di(2-furyl)piperidin-4-one was confirmed as twist-boat with coplanar nitroso orientations by X-ray diffraction studies.\textsuperscript{45}

The N-acyl-2,6-di(2-heteroaryl)-3,5-dimethylpiperidin-4-one (37) was found to prefer flattened half-chair (or sofa) conformations with a small twist along C2-C3 bond.

The formyl group which is comparable to nitroso group was also found to occupy coplanar orientation with respect to the dynamically averaged plane of the piperidine ring in N-formylpiperidin-4-ones. The appearance of two NMR absorptions for N-formylpiperidin-4-ones (38a-j) showed the coplanarity of the N-C=O linkage.
39

\[ R, R' = H \] 

\[ R = Me, R' = H \]

\[ R = Et, R' = H \]

\[ R = i-Pr, R' = H \]

\[ R, R' = Me \]

40

\[ R, R' = H \]

\[ R = Me, R' = H \]

\[ R = i-Pr, R' = H \]

\[ R, R' = Me \]
1.4.3 Stereochemistry of N-Nitroso and N-Acetylpiperidin-4-one Oximes and N-Nitrosopiperidin-4-one Semicarbazones (39 & 40)

The stereochemistry of N-nitroso and N-acetylpiperidin-4-one oximes 39a-g and N-nitrosopiperidin-4-one semicarbazones 40a-d has been analysed by employing $^1$H NMR, $^{13}$C NMR and HETCOR spectral studies. The configurations around C=N bond in the N-nitrosopiperidin-4-one oximes and semicarbazones were determined on the basis of the observation that the α-carbons are more shielded when they are syn to the oxime/semicarbazone function than when they are anti. The C(5) carbons were found to be more shielded (about 5.0±1.0 ppm) compared to C(3) carbons. This shielding of C(5) carbon showed that the oxime hydroxyl group or semicarbazone function is syn to C(5) carbon. The compounds 39a-g and 40a-d were found to be E isomers.

The comparison of the observed vicinal coupling constants and the estimated dihedral angles between the vicinal protons in the N-nitrosopiperidin-4-one oximes & semicarbazones and piperidine-4-one oximes & semicarbazones has revealed that there was twisting about C(2)-C(3) and C(5)-C(6) linkages. The $A^{1,3}$-strain was found to play an important role in deciding the configuration and conformation of the N-nitroso and N-acetylpiperidin-4-one oximes and semicarbazones. Similar systems in which the $A^{1,3}$-strain operated at two positions of the piperidine ring was reported by Harris and...
SCHEM 3

39  a  \( R = R' = R'' = H \)
    b  \( R = R'' = H; \ R' = \text{Me} \)
    c  \( R = R'' = H; \ R' = \text{i Pr} \)
    d  \( R = R' = \text{Me}; \ R'' = \text{H} \)
    e  \( R = \text{H}; \ R' = R'' = \text{Me} \)
41 $X = \text{CO}$; $\text{Ar} = \text{Ph}$
42 $X = \text{CH}_2$; $\text{Ar} = \text{Ph}$
43 $X = \text{CO}$; $\text{Ar} = \text{p-anisyl}$
44 $X = \text{CH}_2$; $\text{Ar} = \text{p-anisyl}$
Spragg. 46 The N-nitrosopiperidin-4-one oximes could exist in equilibrium between four rotamers A, B, C and D (Scheme 3) depending upon the relative orientations of the nitroso and oxime functions. The equilibria C and D were ruled out since the barrier for the rotation about C=N bond was higher.

The twisting of the ring about C(2)-C(3) bond was confirmed by X-ray studies on the isopropyl derivative in which the isopropyl group at C(3) and the phenyl groups at C(2) and C(6) have been found to occupy axial orientations.34 The nitroso group in both the N-nitrosopiperidin-4-one oximes and semicarbazones was found to be coplanar with respect to the dynamically averaged plane of the piperidine ring.

1.4.4 Conformational Preference of Bicyclic Nitrosamines (41-45)

The N-nitroso-2,4-diaryl-3-azabicyclo[3.3.1]nonanes 41-44 can adopt either chair-chair or chair-boat conformations. It was shown to prefer chair-chair conformations with the aryl groups at equatorial positions and the N-nitroso group occupying coplanar orientation. The coupling constants ($J_{1a2a} = J_{4a5a} = 6.5\pm1.2$ Hz) of benzylic proton signals were larger for the N-nitroso-2,4-diphenyl-3-azabicyclo[3.3.1]-nonan-9-ones than for the corresponding parent diphenyl-3-azabicyclo[3.3.1]nonan-9-ones ($J_{2a1a} = J_{5a4a} = 4.4\pm0.2$ Hz). The larger coupling constant of benzylic proton signals was attributed to the flattening of piperidine ring around the nitrogen atom of the nitrosamine.
47 a  $X = \text{CONHPh} ; R, R^1 = H$

b  $X = \text{CONHPh} ; R = \text{Me}, R^1 = H$

c  $X = \text{CONHPh} ; R = \text{Et}, R^1 = H$

d  $X = \text{CONHPh} ; R = \text{i-Pr}, R^1 = H$

e  $X = \text{CONHPh} ; R, R^1 = \text{Me}$

48 a  $X = \text{COPh} ; R, R^1 = H$

b  $X = \text{COPh} ; R = \text{Me}, R^1 = H$

c  $X = \text{COPh} ; R = \text{Et}, R^1 = H$

d  $X = \text{COPh} ; R = \text{i-Pr}, R^1 = H$

e  $X = \text{COPh} ; R, R^1 = \text{Me}$

49  $R, R^1 = H$

50  $R = \text{Me}, R^1 = H$

51  $R = \text{Et}, R^1 = H$

52  $R = \text{i-Pr}, R^1 = H$

53  $R, R^1 = \text{Me}$

54 a  $R = R^1 = H$

b  $R = \text{Me} ; R^1 = H$

c  $R = \text{Et} ; R^1 = H$

d  $R = \text{i-Pr} ; R^1 = H$

e  $R = R^1 = \text{Me}$
The 2,4,6,8-tetraphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (45) was found to adopt chair-boat conformation with all the phenyl groups in equatorial orientation. The corresponding N-nitroso-2,4,6,8-tetraaryl-3,7-diazabicyclo[3.3.1]nonane (46) also preferred chair-boat conformation. In this case, the nitroso group could either be in the chair or boat ring depending on the side from which the reagents approached. Using HETCOR spectral analysis the mononitroso derivative was found to contain the nitroso group in boat ring. A singlet was observed for 46. On the other hand a doublet was expected for the benzylic protons if the nitroso group occurred in chair conformation.

1.4.5 Conformational Preferences of \( N \)-Acylpiperidin-4-ones

The conformational preferences of 2,6-diaryl-\( N \)-acylpiperidin-4-ones (47-53) and 1-acyl-2,7-diphenylhexahydro-1,4-diaarylpyrrolidin-5-ones (54a-e) have been investigated by Pillay and Kumar to understand the ring conformation of substituted \( N \)-acylpiperidin-4-ones and diazepin-5-ones. They have studied the effect of replacement of the hydrogen atom at the nitrogen site by bulky acetyl-, benzoyl- and phenylcarbamoyl group on the \( ^1H \) and \( ^13C \) NMR chemical shifts of the heterocyclic ring system.

The orientation of the acyl group was also ascertained to be coplanar by means of dynamic \( ^1H \) NMR and X-ray data taken for one or two of the compounds. The restricted rotation
about N-C was due to the delocalization of the lone pair of electrons on nitrogen over the carbonyl cleft. The conformation was reported to be 'sofa' for compounds 47a, 47f and 48a and twist-chair conformations for 3-alkyl substituted compounds. The structures of N-benzoyl-3-ethyl-2,6-diphenylpiperidin-4-one and N-phenylcarbamoyl-3-ethyl-2,6-diphenylpiperidin-4-one was proved by the single crystal X-ray diffraction studies and showed that the compounds 47c and 47h preferred twist-chair conformations with pseudo-equatorially oriented phenyl groups.35b

The foregoing discussion revealed the influence of the -X=Y functions at nitrogen in the conformational preferences of piperidines and bicyclic systems. In the present study, it was proposed to investigate the effect of these -X=Y functions in determining the preferential formation of monothioketals. The formation of monothioketals from piperidin-4-ones and 2-mercaptoethanol is analysed on the basis of τ-facial stereoselectivity.

1.5 τ-Facial Stereoselectivity

The nucleophile can selectively approach from either side of the carbonyl group of the six-membered cyclic ketones and result in the predominant formation of one of the products. This selectivity in the nucleophilic addition to carbonyl group is determined by two competitive factors: stereoelectronic factor directing the entering substituent.
into the axial position and a factor depending on the steric hindrance directing the substituent to the equatorial position.

Several models were proposed over the last two decades to explain the stereoelectronic effects in π-facial diastereoselection. The first approach, focused on the analysis of the ground-state properties of the substrates on π-facial diastereoselection.\(^{48a}\) Fukui et al. have shown that the 2p electron density is not distributed symmetrically about the sp\(^2\) plane of a trigonal atom placed in an asymmetric environment. Such nonequivalent orbital extension has been found in the 2-norbornyl radical,\(^{48b}\) norbornene\(^{48c}\) etc., while Anh et al. found nonequivalent distribution of σ-electron density of the carbonyl group in chiral aldehydes and ketones.\(^{49}\) It has been proposed that reactions such as electrophilic additions to alkenes are controlled by the interaction of the electrophile's LUMO with the chiral substrate's HOMO which preferentially occurred on the sp\(^2\) face. The reverse is true for nucleophilic addition reactions.\(^{50}\) Similar analyses were employed in the interpretation of stereochemistry of reactions in cyclohexane based systems (cyclohexanones, methylenecyclohexanes, thianes) with one trigonal atom in the ring,\(^{50b}\) effect of remote substituents on stereochemistry of hydride reduction of adamantanes\(^{50c}\) etc. In the attempt to demonstrate nonequivalent distribution of σ-electron density in
$R = \text{Me, Ph, } t-\text{Bu}$

$X = \text{CO, CH}_2$

$Y = \text{Cl, Ph}$

CHART 1
asymmetric environment by experimental methods, Pacquette et al. undertook a systematic examination of the spectroscopic evidence and face-selective complexation of Lewis acids.\textsuperscript{50d}

Klein\textsuperscript{51} proposed that hyperconjugation of the ring C–C bonds with the π system forced nonequivalent distribution of π electron density. As a result, the HOMO orbital would be more extended on the equatorial face of the trigonal center and the electrophilic reagent would prefer equatorial attack for both steric and stereoelectronic reasons whereas the nucleophilic reagents would prefer the axial approach since the LUMO orbital is more extended on the axial face of the trigonal center.

Hudec\textsuperscript{52} offered a new perspective by proposing that the preferred direction is controlled by deviations in the 'twist-angle', which is the angle by which the axis of the π* orbital of the carbonyl carbon atom is twisted towards the substituent, making the two faces diastereotopic. If the angle is positive, the nucleophile would preferably approach from the side of the substituent and conversely, if the angle is negative, attack would predominantly come from the opposite side.

1.5.1 Cieplak Model

The selectivity observed in most of the reactions at the carbonyl carbon in enantiomeric 3-substituted cyclohexanone (55) and adamantanone (56) has been explained by Cieplak\textsuperscript{53}. 

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In his model (Chart 1), the dominating interactions in the transition state are between the occupied σ bond and the σ* orbital of the forming bond between nucleophile and the carbonyl carbon atom. Cieplak's model is based on the assumption that in the transition state electrons are shifted into the antibonding orbital of an incipient bond. Thus the approach of the nucleophile to the carbonyl, syn or anti to the substituent was considered to be controlled by the electron density of the adjacent antiperiplanar bonds to the carbonyl π-system. Cieplak postulate states that an incoming nucleophile will add to the carbonyl group from the face that allows for the greater antiperiplanar hyperconjugative stabilization from an adjacent vicinal σ-bond. Thus an electron-withdrawing group at C(3) of cyclohexanone (55) enhanced the axial attack and electron-donating R group, promoted equatorial attack. Arguments in favour of Cieplak proposal came from several authors and were based on experimentally observed substituent effects in nucleophilic addition reactions of carbonyl compounds.54

The reagent PhSCH₂Li added on to 3-(trimethylsilyl)-cyclohexanone (57) from the less hindered equatorial side in the ratio 90:10. The reagent Ph(SO)(NMe)CH₂Li wherein two electron-withdrawing groups are attached to the sulfur atom of the nucleophile attacked the same ketone with a slight preference for the axial side (45:55) and finally when the SiMe₃ group was exchanged for the CF₃ group, a strong
preference (17:83) for the hindered axial approach resulted. Danishefsky and Langer observed a complete reversal of the usual preference of L- and K-selectrides for the less hindered equatorial approach to the six-membered cyclic ketones 58 and 59, apparently as a result of the replacement of a methyl group by a methoxy group.\textsuperscript{54c}

The metal hydride reduction and organometallic additions of 3-alkyl and 3,5-dialkylcyclohexanones resulted in an increase in the proportion of the equatorial approach due to an increase in the electron-donating power of the $\sigma_{CC}$ bonds.\textsuperscript{55} This observation suggested a selective stabilization of the equatorial transition state in compliance with Cieplak prediction.

Electron-withdrawing substitution, which lowers $\Sigma (\sigma^*_{\text{d}})$ produced a predominance of the axial approach, overriding nucleophiles steric demand. The Cieplak's preposition is further supported by le Noble's work on 5-substituted adamantan-2-one (56). In the case of 5-substituted adamantanone 56, the two faces of the carbonyl group are sterically equivalent. It has been found that electron-withdrawing groups at C(5) directed nucleophiles to the \textit{syn} side in carbonyl addition and electron-donating groups directed them to the \textit{anti} side.\textsuperscript{56} All 5-halogen substituents caused greater electron density in the 1,8 & 3,10 bonds than in the 1,9 & 3,4 bonds and therefore the opportunity of delocalization is
greater in the syn approach. The above ketone with electronwithdrawing substituents at C(5) position which were reduced to a mixture of epimeric alcohols, achieved in quantitative yields with several reducing agents, gave predominantly the Eisomer. The epoxidation of 5-fluoro-2-methyleneadamantane (60) with MCPA, gave a mixture of two oxiranes 60a and 60b in the ratio 66:34. The predominant isomer 60a had the Z-configuration.

Scope and Limitation of the Study

The foregoing literature survey revealed that many models have been proposed to explain the stereoselectivity observed during the nucleophilic additions to carbonyl groups. Of these, Cieplak's model was found to explain the stereoselectivity in the most satisfactory manner. The conformational preferences of the heterocycles were decided by the nature of the substituents at nitrogen viz., -NO, -COCH₃, -CHO etc. In order to correlate the influence of these substituents in the formation of the spiro ring at carbonyl carbon and to study the stereoselectivity during the addition reactions, several 3-alkyl substituted 2,6-diphenylpiperidine, N-methyl-2,6-diphenylpiperidine, N-nitroso-2,6-diphenylpiperidine, N-acetyl-2,6-diphenylpiperidine and N-nitroso-2,4-diphenyl-3-azabicyclo[3.3.1]nonane monothioketals have been synthesised. Their stereochemistry has been studied using ¹H NMR, ¹³C NMR, ¹H-¹H HOMOCOSY, dynamic NMR and X-ray
diffraction studies. To confirm further the assigned configuration of monothioketals, the sulfoxides were synthesised and their stereochemistry was also studied.

The limitation of the present study is that the ratio of the isomers obtained in the nucleophilic addition reactions could not be determined precisely due to practical difficulties encountered. But the facial selectivity during the addition of 2-mercaptoethanol to the substituted piperidin-4-ones was examined on the basis of the percentage yield calculated for the isolated major isomers. The results were rationalized in terms of the currently discussed model of stereoelectronic effect (Cieplak model) in π-facial stereoselection.
SCHEME 4

61 $\text{Ar} = \text{Ph}; \text{R} = \text{H}$
62 $\text{Ar} = \text{Ph}; \text{R} = \text{CH}_3$
63 $\text{Ar} = \text{Ph}; \text{R} = \text{I-Pr}$
64 $\text{Ar} = \text{p-NO}_2\text{C}_6\text{H}_4; \text{R} = \text{CH}_3$
65 $\text{Ar} = \text{p-Tolyl}; \text{R} = \text{CH}_3$

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