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2-Isoxazolidineethanols: An NMR study of the effect of intramolecular H-bonding on the population of nitrogen invertomers and inversion process

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Abstract

A series of (*βR*,*5R*)- and (*βR*,*5S*)-2,5-disubstituted isoxazolidines: 5-(substituent)-β-phenyl-2-isoxazolidineethanols, have been prepared by asymmetric nitrone cycloaddition reactions and their NMR spectra recorded over a wide range of temperatures. The spectra at low temperatures indicate the presence of the (*βR*,*5S*) diasteromer almost exclusively as a single invertomer having *trans* disposition of the substituents at N(2) and C(5), while the (*βR*,*5R*) diasteromer remained as a mixture of two interconverting invertomers in deuterated chloroform. The effect of H-bonding – intramolecular in $CDCl_3$ and intermolecular in CD_3OD – on the population ratio of the invertomers and nitrogen inversion process has been investigated. The nitrogen inversion barriers are determined using complete line-shape analysis, and their dependence on solvent is discussed. Due to steric factor the *trans*-invertomers are found to be more stable than their *cis* counterparts.

Keywords: Isoxazoldines; Nitrogen inversion; Invertomers; Inversion barriers

1. Introduction

Among a plethora of functional groups the nitrone functionality has etched a place of distinction in the synthesis of a great many natural products of biological interest [1]. In recent years, the focus has been shifted towards asymmetric nitrone cycloaddition reactions [2–7]. Intramolecularly H-bonded (*R*)-chiral nitrone as shown in Scheme 1 is receiving increasing attention and becoming very popular owing to its efficacy in transferring chirality to the newly created stereocenters at C(5) of the cycloadducts isoxazolidines **1** and **2** in a highly stereoselective manner [8,9]. The facile reductive cleavage of the isoxazolidines provides a simple and efficient access to a variety of synthetically important chiral 1,3-aminoalcohols. However, it is often difficult to assign the configuration at C(5) by spectroscopic analysis owing to complications arising out of slow nitrogen inversion process involving *cis*- and *trans*-invertomers as well as the pseudorotation in a five-membered ring.

The previous studies [10–12] of nitrogen inversion in bicyclic isoxazolidines have greatly contributed to the understanding of several reaction processes involving isoxazolidines. The presence of heteroatom oxygen slows down the lone pair inversion in nitrogen to such an extent that at ambient or lower temperatures the presence of two interconverting diastereomeric isoxazolidines *trans* and *cis* could be identified by NMR spectroscopy. We have prepared a series of 2,5-disubstituted isoxazolidines **1** and **2** using nitrone-alkene cycloaddition reactions to study the configurational aspects as well as nitrogen inversion process by NMR spectroscopy (Scheme 2). The study would provide us with the opportunity to ascertain the stereochemistry of the cycloaddition products and examine the effect of H-bonding – intramolecular in $CDCl_3$ and intermolecular in CD_3OD – on the population ratio of the invertomers: *trans*-**1** versus *cis*-**1** and *trans*-**2** versus *cis*-**2** (Scheme 2).

2. Experimental

2.1. Compounds studied

A total of 12 compounds have been studied in the current work. The structures of these compounds are given in Scheme 2.

2.2. Physical methods

The variable temperature ^1H NMR spectra were recorded on a JEOL Lambda NMR spectrometer operating at 500.0 MHz.

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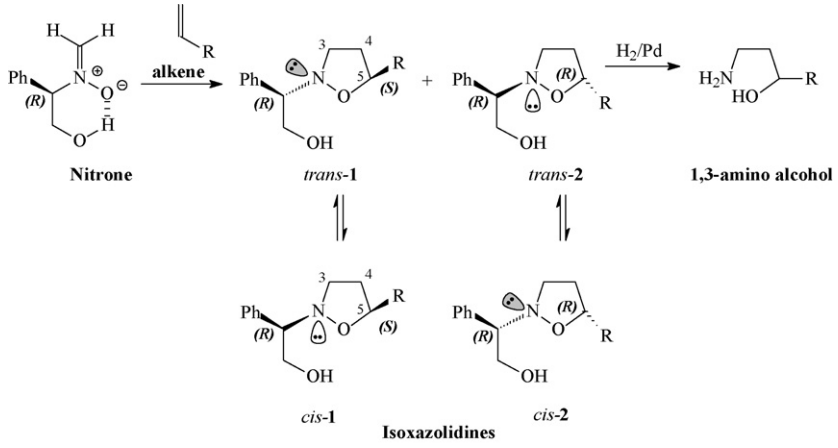


Scheme 1.

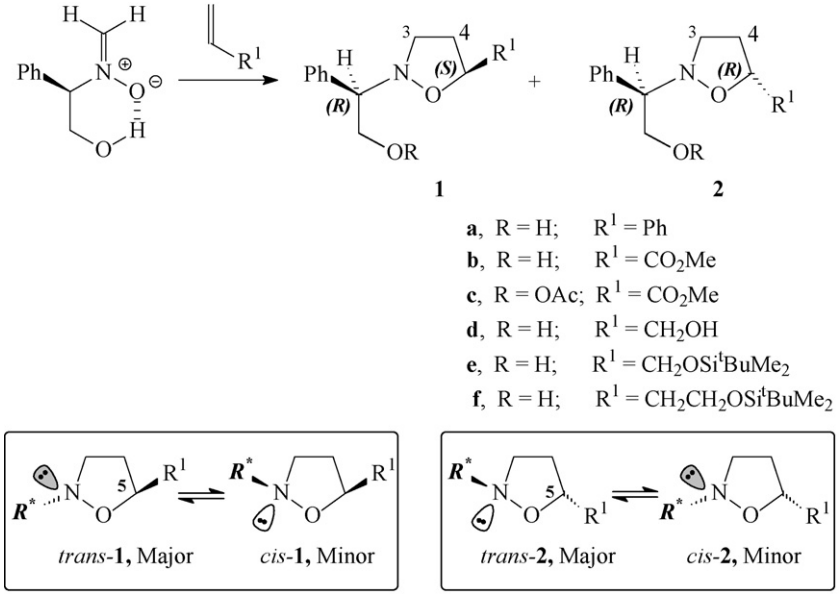
Most of the compounds were studied as 25 mg/cm^3 solutions in $CDCl_3$ and CD_3OD with TMS as internal standard. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ using TMS as internal standard on a JEOL LA 500 MHz spectrometer. Multiplicities of the carbons were determined using DEPT experiments. Elemental analysis was carried out on a EuroVector Elemental Analyzer Model EA3000. IR spectra were recorded on a Perkin-Elmer 16F PC FTIR spectrometer. X-ray crystallographic analysis was carried out on a Bruker-AXS Smart Apex system equipped with graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å). Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland).

2.3. Synthesis of isoxazolidines (*1* and *2*)

The isoxazolidines (**1**, **2**) **a**, **b**, **d**–**f** were prepared using procedure as described [13]. The optically pure (*R*)-nitrone underwent cycloaddition reactions with monosubstituted alkenes gave in each case a mixture of two diastereomeric isoxazolidines **1** and **2** having (*R*)(*S*) and (*R*)(*R*) configuration, respectively (Scheme 2). Since the configuration of **2b** is known by X-ray analysis as (*R*)(*R*), the **1b** must then have the (*R*)(*S*) configuration. The obtainment of the acetyl derivatives **1c** and **2c** from **1b** and **2b** thus assures the stereochemistry of the former pair (*vide infra*). The C(5) configuration of most of the other isoxazolidines has been established by chemical conversion to known structures [13]. The low temperature ^1H and ^{13}C NMR data of these compounds are given below.

2.3.1. (βR,5S)-5-Phenyl-β-phenyl-2-isoxazolidineethanol (*1a*) and (βR,5R)-5-phenyl-β-phenyl-2-isoxazolidineethanol (*2a*)

The isoxazolidines were prepared and purified by chromatography to obtain a pure sample of a non-separable mixture of isomers **1a** and **2a**, in a ratio of 73:27 [13]. This mixture was used for the study. Careful analysis of the spectrum, measured in $CDCl_3$, at low temperature revealed the presence of two invertomers for each of the isoxazolidines **1a** and **2a**. The spectrum



Scheme 2. Compounds studied.

was analyzed to obtain the signals for the individual isoazolidine/invertomer as given below.

1a—*Major invertomer*: δ_H($CDCl_3$, −30 °C) 2.20 (1H, m), 2.77 (1H, m), 2.98 (1H, m), 3.28 (1H, m), 3.70 (1H, OH), 3.76 (1H, m), 4.05 (1H, m), 4.22 (1H, m), 5.39 (1H, t, J = 7.4 Hz), 7.40 (10H, m.; δ_C($CDCl_3$, −30 °C) 36.74, 53.94, 68.73, 70.83, 78.93, 128.8 (2C) and 129.8 (2C), 137.68 and 140.59.

Minor invertomer: C5(H) signal for minor invertomer appear at 4.97 ppm (t, J = 7.5 Hz) in a ratio of 94:6. The ^{13}C spectrum also revealed the presence of weak signals for the minor invertomer of **1a** at 37.22, 51.17, 63.51, 70.28, 78.59 ppm.

In CD_3OD (−30 °C), several nonoverlapping minor signals indicating the major/minor in a ratio of 79:21. C(5)H of the major and minor appeared at δ 5.29 and 4.86 ppm, respectively.

2a—*Major invertomer*: δ_H($CDCl_3$, −30 °C) 2.1 (1H, m), 2.6 (1H, m), 2.65 (1H, m), 3.15 (1H, m), 3.55 (1H, m), 3.70 (1H, OH), 4.00 (1H, m), 4.17 (1H, m), 5.16 (1H, t, J = 7.5 Hz), 7.4 (10H, m); δ_C($CDCl_3$, −30 °C) 36.26, 55.07, 68.42, 74.17, 80.22, 128.8–129.8 overlapping signals of aromatic carbons, 137.57 and 140.13.

Minor invertomer: C5(H) signal for the minor invertomer of minor isomer **2a** appeared at 4.72 ppm (t, J = 7.1 Hz) in a ratio of 91:9. The ^{13}C spectrum also revealed the presence of weak signals for the minor invertomer at 37.71, 52.13, 63.68, 71.35, 78.28 ppm.

In CD_3OD (−30 °C), several nonoverlapping minor signals indicating the major/minor of **2a** in a ratio of 85:15. C(5)H of the major and minor appeared at δ 5.03 and 4.83, respectively.

*2.3.2. (1R,5S)-Methyl 2-(2-hydroxy-1-phenylethyl)-5-isoxazolidinecarboxylate (**1b**) and (1R,5R,)-methyl 2-(2-hydroxy-1-phenylethyl)-5-isoxazolidinecarboxylate (**2b**)*

The isoxazolidines were prepared and separated by chromatography to obtain pure samples of isomers **1b** and **2b** [13]. Spectra, measured in $CDCl_3$, at low temperature revealed the presence of a single invertomer for **1b**, and two invertomers for **2b**.

1b—*A single invertomer*: δ_H($CDCl_3$, −30 °C) 2.42 (1H, m), 2.61 (2H, m), 3.01 (1H, m), 3.69 (1H, OH), 3.78 (1H, m), 3.83 (3H, s), 3.99 (2H, m), 4.76 (1H, dd, J = 4.0 and 9.5 Hz), 7.33 (5H, m); δ_C($CDCl_3$, −30 °C) 32.30, 52.50, 52.70, 67.10, 71.26, 74.37, 127.9 (2C), 128.1, 128.6 (2C), 138.19, 173.08. ^{1}H as well as ^{13}C NMR spectra did not reveal the presence of a minor invertomer. The proton signals were sharp even at room temperature.

In CD_3OD (−30 °C), several nonoverlapping minor signals indicating the major/minor in a ratio of 89:11. C(5)H of the major and minor appeared at δ 4.78 and 4.35, respectively. Methyl singlets appeared at 3.75 (major) and 3.66 (minor).

2b—*Major invertomer*: δ_H($CDCl_3$, −30 °C) 2.46 (2H, m), 3.12 (2H, m), 3.85 (3H, s), 3.65–4.40 (4H, several m), 4.71 (1H, t, J = 7.6 Hz), 7.30 (5H, m); δ_C($CDCl_3$, −30 °C) 32.39, 52.91, 53.01, 68.07, 73.08, 76.68, 128.20 (2C), 128.80 (2C), 129.55, 138.26, 172.68.

Minor invertomer: δ_H($CDCl_3$, −30 °C) 2.46 (2H, m), 2.62 (1H, m), 2.92 (1H, m), 3.81 (3H, s), 3.65–4.40 (4H, complex m), 4.54 (1H,t, J = 6.6 Hz), 7.30 (5H, m); δ_C($CDCl_3$, −30 °C) 33.01, 48.90, 52.64, 63.59, 68.87, 72.93, 127.69 (2C), 128.20 (2C), 128.80, 135.20, 174.12. Several nonoverlapping minor signals indicated the major/minor invertomers in a ratio of 55:45.

In CD_3OD (−30 °C), several nonoverlapping minor signals indicating the major/minor in a ratio of 70:30. C(5)H of the major and minor appeared at δ 4.63 and 4.48, respectively. Methyl singlets appeared at 3.76 (major) and 3.69 (minor).

*2.3.3. (1R,5S)-Methyl 2-(2-acetyloxy-1-phenylethyl)-5-isoxazolidinecarboxylate (**1c**) and (1R,5R)-methyl 2-(2-acetyloxy-1-phenylethyl)-5-isoxazolidinecarboxylate (**2c**)*

1c: A solution of the cycloadduct **1b** (100 mg) and acetic anhydride (0.5 g) in $CHCl_3$ (2 cm^3) was heated in a closed vessel under N_2 at 70 °C for 5 h. After removal of the solvent and excess acetic anhydride by a gentle stream of N_2, the residual liquid was taken up in ether (30 cm^3) and washed with 5% $NaHCO_3$ solution (10 cm^3). The organic layer was concentrated and chromatographed using a mixture of hexane/ether as eluant to afford the acetyl derivative **1c** in 75% yield as a colourless liquid—found: C, 61.2; H, 6.4; N, 4.7.; $C_{15}H_{19}NO_5$ requires C, 61.42; H, 6.53; N, 4.78%; $\nu_{max.}$(neat) 3030, 2954, 2850, 1731, 1495, 1454, 1383, 1231, 1046, 833, 760 and 703 cm^{-1}.

Major invertomer: δ_H($CDCl_3$, −30 °C) 1.99 (3H, s), 2.42 (1H, m), 2.61 (1H, m), 2.74 (1H, m), 3.02 (1H, m), 3.80 (3H, s), 3.90 (1H, m), 4.38 (1H, m), 4.72 (1H, dd, J = 3.95, 11.0 Hz), 4.79 (1H, dd, J = 4.25, 9.75), 7.33 (5H, m); δ_C($CDCl_3$, −30 °C) 21.10, 31.87, 52.10, 52.70, 66.50, 68.46, 75.07, 128.24 (2C), 128.35, 128.61 (2C), 137.77, 171.09, 172.45.

Minor invertomer: δ_H($CDCl_3$, −30 °C) minor invertomer revealed the presence of nonoverlapping acetyl protons at δ 2.09, CO_2Me at 3.71 and C(5)H at 4.50 ppm. The ratio of the invertomers was found to 87:13 by integration. The spectrum at −30 °C revealed the presence of the following ^{13}C signals for the nonaromatic carbons of the minor invertomer: δ_C($CDCl_3$, −30 °C) 21.08, 33.78, 52.10, 52.47, 66.15, 69.30, 74.67.

In CD_3OD (−30 °C), several nonoverlapping minor signals indicating the major/minor in a ratio of 91:9. Acetyl Me of the major and minor appeared at δ 1.89 and 2.01, respectively. Methyl singlets of CO_2Me appeared at 3.74 (major) and 3.65 (minor).

2c: The cycloadduct **2b** was acetylated using procedure as discussed above to give **2c** in 73% yield as a colourless liquid—found: C, 61.3; H, 6.5; N, 4.7; $C_{15}H_{19}NO_5$ requires C, 61.42; H, 6.53; N, 4.78%); $\nu_{max.}$(neat) 3030, 2992, 2955, 2853, 1738, 1444, 1380, 1228, 1045, 915, 842, 759, 733 and 705 cm^{-1}.

Major invertomer: δ_H($CDCl_3$, −30 °C) 2.0 (3H, s), 2.40 (1H, m), 2.63 (1H, m), 2.84 (1H, td, J = 6.4, 10.7 Hz), 3.06 (1H, dt, J = 7.0, 10.7 Hz), 3.82 (3H, s), 4.09 (1H, dd, J = 3.5, 6.3 Hz), 4.54 (1H, dd, J = 6.0, 11.0 Hz), 4.66 (2H, m), 7.37 (5H, m); δ_C($CDCl_3$, −30 °C) 21.16, 32.65, 52.59, 52.74, 65.98, 69.15, 76.40, 128.24 (2C), 128.35, 128.61 (2C), 137.80, 171.12, 172.94.

Minor invertomer: δ_H($CDCl_3$, −30 °C) 2.09 (3H, s), 2.54 (2H, m), 2.72 (1H, q, J = 8.4 Hz), 3.49 (1H, m), 3.77 (3H, s), 4.01 (1H, dd, J = 4.6, 7.0 Hz), 4.32 (1H, dd, J = 7.3, 11.9 Hz), 4.36 (1H, dd, J = 4.9, 11.9 Hz), 4.50 (1H, m), 7.37

(5H, m). The nonoverlapping signals for minor invertomer: δ_C($CDCl_3$, −30 °C) 33.09, 65.77, 73.63, 137.29, 170.99, 173.21. Major/minor ratio was determined to be 70:30.

In CD_3OD (−30 °C), several nonoverlapping minor signals indicating the major/minor in a ratio of 79:21. Acetyl Me of the major and minor appeared at δ 1.90 and 2.00, respectively. Methyl singlets of CO_2Me appeared at 3.68 (major) and 3.60 (minor)

2.3.4. (βR,5S)-5-(Hydroxymethyl)-β-phenyl-2-isoxazolidineethanol (**1d**) and (βR,5R)-5-(hydroxymethyl)-β-phenyl-2-isoxazolidineethanol (**2d**)

The isoxazolidines **1d** and **2d** were prepared by $LiAlH_4$ reduction of the isoxazolidines **1b** and **2b**, respectively [13]. Spectra, measured in $CDCl_3$, at low temperature revealed the presence of a single invertomer for **1d**, and two invertomers for **2d**.

1d—*A single invertomer*: δ_H($CDCl_3$, −30 °C) 2.11 (1H, m), 2.35 (1H, m), 2.73 (1H, m), 3.03 (1H, td, J = 7.8, 10.7 Hz), 3.67 (1H, dd, J = 4.5, 12.0 Hz), 3.75–4.05 (5H, m), 4.11 (1H, dd, 6.9, 11.1 Hz), 4.52 (1H, dtd, J = 2.15, 4.7, 8.7 Hz), 7.32 (5H, m). δ_C($CDCl_3$, −30 °C) 28.81, 53.80, 64.50, 67.89, 71.28, 78.20, 127.82 (2C), 128.25, 128.79 (2C), 137.59.

In CD_3OD (−30 °C), several nonoverlapping minor signals including C(5)H at δ 4.39 (major) and 4.25 (minor) indicated the major/minor in a ratio of 88:12.

2d—*Major invertomer*: δ_H($CDCl_3$, −30 °C) 2.19 (2H, app. q, J = 7.2 Hz), 2.67 (1H, td, J = 7.1, 10.4 Hz), 3.02 (1H, td, J = 7.1, 10.4 Hz), 3.64 (1H, dd, J = 3.7, 12.5 Hz), 3.73 (1H, d, J = 11.6 Hz), 3.92 (1H, dd, J = 2.2, 8.9 Hz), 4.20 (1H, dd, 8.2, 11.9 Hz), 4.0–4.4 (2H, br, OHs), 4.34 (1H, m), 7.32 (5H, m); δ_C($CDCl_3$, −30 °C) 28.49, 54.39, 62.58, 68.40, 72.80, 80.36, 127.75 (2C), 128.22, 128.80 (2C), 137.75.

Following are the nonoverlapping signals for the Minor invertomer: δ_H($CDCl_3$, −30 °C) 2.03 (1H, m), 2.09 (1H, m), 2.85 (1H, m), 3.33 (1H, m), 3.55 (1H, m), 3.86 (1H, m), 4.07 (1H, m), 4.12 (1H, m); δ_C($CDCl_3$, −30 °C) 29.94, 52.06, 63.68, 71.32, 80.26, 128.45, 128.99, 136.72. Major/minor ratio was determined to be 84:16.

In CD_3OD (−30 °C), several nonoverlapping minor signals including C(5)H at 4.17 (major) and 4.05 (minor) indicated the major/minor in a ratio of 90:10.

2.3.5. (βR,5S)-5-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-β-phenyl-2-isoxazolidineethanol (**1e**) and (βR,5R)-5-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-β-phenyl-2-isoxazolidineethanol (**2e**)

The isoxazolidines were prepared and separated by chromatography to obtain pure samples of isomers **1e** and **2e** [13]. Spectra, measured in $CDCl_3$, at low temperature revealed the presence of a single invertomer for **1e**, and two invertomers for **2e**.

1e—*A single invertomer*: δ_H($CDCl_3$, −30 °C) 0.093 (6H, s), 0.91 (9H, s), 1.92 (1H, m), 2.31 (1H, m), 2.73 (1H, m), 3.00 (1H, td, J = 7.6, 10.6 Hz), 3.65 (2H, m), 3.74 (1H, dd, J = 6.3, 10.6 Hz), 3.87 (1H, d, J = 5.8 Hz), 4.15 (1H, dd, J = 7.65, 11.6 Hz), 4.46 (1H, m), 7.32 (5H, m); δ_C($CDCl_3$, −30 °C) (–)5.42, 18.25, 25.76 (3C), 29.37, 53.32, 64.44, 68.97, 70.92, 78.22, 127.81 (2C), 128.01, 129.13 (2C), 137.85.

In CD_3OD (−30 °C), several nonoverlapping minor signals including the *t*-Bu singlets at 0.96 (major) and 0.91 (minor) and C(5)H at 4.31 (major) and 4.15 (minor) indicated the major/minor of **1e** in a ratio of 87:13.

2e—*Major invertomer*: δ_H($CDCl_3$, −30 °C) 0.11 (3H, s), 0.12 (3H, s), 0.93 (9H, s), 2.04 (1H, m), 2.21 (1H, m), 2.58 (1H, q, J = 8.0 Hz), 2.98 (1H, m), 3.65–3.85 (5H, m), 4.13 (1H, m), 4.29 (1H, m), 7.32 (5H, m); δ_C($CDCl_3$, −30 °C) (–)5.43, (–)5.28, 18.24, 25.76 (3C), 29.31, 54.25, 64.30, 68.55, 73.65, 79.27, 127.70 (2C), 128.08, 129.23 (2C), 137.96. Major/minor ratio was determined to be 97:3 as indicated by the presence of minor ^{t}Bu singlet.

In CD_3OD (−30 °C), several nonoverlapping minor signals including the *t*-Bu singlets at δ 0.94 (major) and 0.84 (minor) in a ratio 81:19.

2.3.6. (βR,5S)-5-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-β-phenyl-2-isoxazolidineethanol (**1f**) and (βR,5R)-5-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-β-phenyl-2-isoxazolidineethanol (**2f**)

The isoxazolidines were prepared and separated by chromatography to obtain pure samples of isomers **1f** and **2f** [13]. Spectra, measured in $CDCl_3$, at low temperature revealed the presence of a single invertomer for **1f**, and two invertomers for **2f**.

1f—*A single invertomer*: δ_H($CDCl_3$, −30 °C) 0.082 (3H, s), 0.087 (3H, s), 0.91 (9H, s), 1.84 (2H, m), 1.91 (1H, m), 2.45 (1H, m), 2.80 (1H, m), 3.05 (1H, m), 3.6–3.8 (4H, m), 3.89 (1H, d, J = 6.1 Hz), 4.14 (1H, dd, J = 8.0, 11.1 Hz), 4.56 (1H, m), 7.32 (5H, m); δ_C($CDCl_3$, −30 °C) (–)5.50 (2C), 18.29, 25.81 (3C), 33.23, 37.61, 53.25, 59.92, 69.05, 70.88, 74.59, 127.78 (2C), 128.07, 128.69 (2C), 137.89.

In CD_3OD (−30 °C), several nonoverlapping minor signals including the *t*-Bu singlets at 0.83 (major) and 0.76 (minor) indicated the presence of the invertomers of **1f** in a ratio 82:18.

2f—*Major invertomer*: δ_H($CDCl_3$, −30 °C) 0.086 (6H, s), 0.91 (9H, s), 1.87 (3H, m), 2.31 (1H, m), 2.51 (1H, m), 2.98 (1H, m), 3.6–3.8 (5H, m), 4.14 (1H, m), 4.29 (1H, m), 7.32 (5H, m); δ_C($CDCl_3$, −30 °C) (–)5.50 (2C), 18.40, 25.96 (3C), 33.35, 38.11, 54.42, 60.41, 69.02, 71.08, 74.12, 127.81 (2C), 127.89, 128.76 (2C), 137.84.

Minor invertomer: the presence of the minor invertomer was displayed by minor signals at δ 0.87 (^{t}Bu) and 4.29 (C-5, H) in a 92:8 ratio.

In CD_3OD (−30 °C), several nonoverlapping minor signals including the *t*-Bu singlets at 0.83 (major) and 0.76 (minor) indicated the presence of the invertomers in a ratio of 93:7.

2.4. Inversion barrier calculations

The variable temperature ^{1}H NMR spectra were recorded on a JEOL Lambda NMR spectrometer operating at 500.0 MHz. Most of the compounds were studied as 25 mg/cm^3 solutions in $CDCl_3$ and CD_3OD with TMS as internal standard. Simulations of exchange-affected proton spectra for all compounds were car-

ried out using a computer program AXEX [14], corresponding to a two non-coupled sites exchange with unequal populations. For **1b** (CD_3OD), **2b** ($CDCl_3$ and CD_3OD), **1c** ($CDCl_3$), **2c** ($CDCl_3$), C(5)CO_2Me resonances were utilized, whereas for **1c** (CD_3OD), and **2c**(CD_3OD), the OAc singlet signals were utilized. For **1e** (CD_3OD), **2e** (CD_3OD) and **1f** (CD_3OD) the *tert*-butyl singlets were utilized. Simulations of exchange-affected triplets were carried out by modifying the two-site exchange program [15]. The first order coupling to these protons is simply assumed as giving overlapping two site exchanges with the same population ratio and equal rates of exchange. Similar simulation was carried out for the quartet signals of a C(3)H in **2d** ($CDCl_3$).

3. Results and discussion

Each nitrone–alkene cycloaddition afforded a separable mixture of diastereomeric isoxazolidines **1** and **2** having (*R*,*S*) and (*R*,*R*) configurations [13], respectively (priority based on assuming R^1 as oxygenated substituents). Since the nitrone is optically pure having 'R' configuration, the isoxazolidines differ only in the configuration of the C(5) substituents. During the course of a structural investigation of the isomeric isoxazolidines **1**b and **2b** (R = CO_2Me) it was interesting to observe the presence of a single invertomer for one of the isoxazolidines, while the other remained as an equilibrating mixture of two invertomers (*cis* and *trans*) in a 55:45 ratio at −30 °C in $CDCl_3$. This is surprising since a look at their structures seems to covey that *trans*-**1** and *trans*-**2** (or *cis*-**1** and *cis*-**2**) (Scheme 1) should have comparable steric environments, and as such a large discrepancy in the population ratio of the invertomers in **1b** and **2b** is quite unexpected. The current study helped us to provide a rational for this observation (*vide infra*).

The nitrogen inversions barriers are determined using NMR band shape analysis. Slow nitrogen inversion in most of the isoxazolidines, especially in the series **2**, has been observed to give broadened peaks in ^{1}H and ^{13}C spectra recorded at ambient temperature. On lowering the temperature, the spectral lines become sharper and show two distinct forms of the compound. The ^{13}C chemical shifts were assigned on the basis of DEPT experiment results, general chemical shifts arguments and consideration of substituent effects, and are given in Table 1.

Around −10 °C, the ^{1}H NMR spectra of these compounds show well-separated signals for the two invertomers. Integration of the relevant peaks gives the population trends in these systems. The proton spectra were used in the calculation of barriers in all compounds. The complete band shape analysis yielded the rate constants and the free energy of activation using Eyring equation. The activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were calculated from plots of ln(k/T) versus 1/T. It is well known [16] that NMR band shape fitting frequently gives rather large but mutually compensating errors in $\Delta H^{\neq}$ and $\Delta S^{\neq}$ and as such their values are not reported here. However, band shape fitting is viewed as a method of getting rather accurate values of $\Delta G^{\neq}$ (probably within ±0.3 kJ/mol) in the vicinity of the coalescence

Table 1
^{13}C NMR chemical shifts of compounds studied in $CDCl_3$ at −30 °C

Compound		C-3	C-4	C-5	N-C
1a	Major (*trans*)	53.94	36.74	78.93	70.83
	Minor (*cis*)	51.17	37.22	78.59	70.28
2a	Major (*trans*)	55.07	36.26	80.22	74.17
	Minor (*cis*)	52.13	37.71	76.28	71.35
1b	(*trans*)	52.70	32.30	74.37	71.26
2b	Major (*trans*)	52.91	32.39	76.68	73.08
	Minor (*cis*)	48.90	33.01	72.93	68.87
1c	Major (*trans*)	52.10	31.87	75.07	68.46
	Minor (*cis*)	52.10	33.78	74.67	69.30
2c	Major (*trans*)	52.59	32.65	76.40	69.15
	Minor (*cis*)	52.59	33.09	73.63	69.15
1d	(*trans*)	53.80	28.81	78.20	71.28
2d	Major (*trans*)	54.39	28.49	80.36	72.80
	Minor (*cis*)	52.06	29.94	77.40	71.32
1e	(*trans*)	53.32	29.37	78.22	70.92
2e	(*trans*)	54.25	29.31	79.27	73.65
1f	(*trans*)	53.25	33.23	74.59	70.88
2f	(*trans*)	54.42	33.35	74.12	71.08

Table 2
Free energy of activation ($\Delta G^{\neq}$) for nitrogen inversion, ratio of the invertomers, and standard free energy change (ΔG°) for major ↔ minor isomerization in $CDCl_3$ and CD_3OD

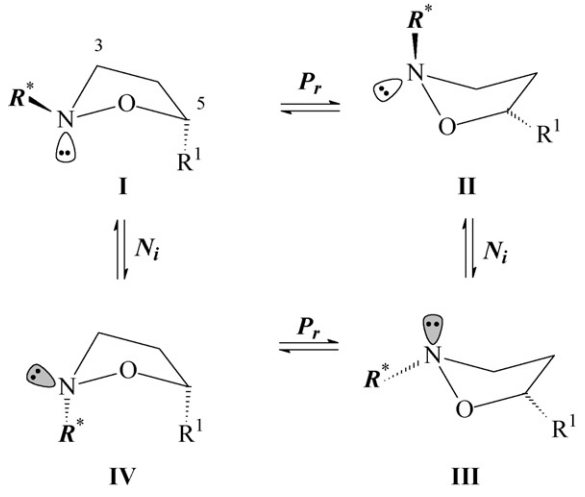
Compound	$CDCl_3$			CD_3OD		
	$\Delta G^{\neq}$ (kJ/mol)[a]	Invertomer ratio	ΔG° (kJ/mol)[b]	$\Delta G^{\neq}$ (kJ/mol)[a]	Invertomer ratio	ΔG° (kJ/mol)[b]
1a	62.2	94:6	+5.3	–	79:21	–
2a	61.2	91:9	+4.5	–	85:15	–
1b	–	100:∼0	–	60.3	89:11	+4.0
2b	55.4	55:45	+0.38	58.8	70:30	+1.6
1c	60.1	87:13	+3.7	59.9	91:9	+4.5
2c	58.7	70:30	+1.7	59.6	79:21	+2.6
1d	–	100:∼0	–		88:12	
2d	59.6	84:16	+3.2	63.0	90:10	+4.3
1e	–	100:∼0	–	61.6	87:13	+3.7
2e	–	97:3	+6.9	60.6	81:19	+2.8
1f	–	100:∼0	–	60.4	82:18	+2.9
2f	–	92:8	–	–	93:7	–

[a] At 0 °C.
[b] At −30 °C.

temperature. The $\Delta G^{\neq}$ values calculated at 0 °C are reported in Table 2, along with the invertomer and ΔG° values.

Both the *cis*-1,3-dimethylcyclopentane and *cis*-1,3-dimethylcyclohexane are more stable than their *trans* counterparts by an enthalpy difference of 2.3 kJ/mol and 7.1 kJ/mol, respectively. The slight preference for the *cis* isomer in cyclopentane disappears in heterocyclic systems like isoxazolidines, where the presence of two heteroatoms in the ring skeleton would shorten the bond lengths thus augmenting the steric congestion between the *cis* substituents. The 2,5-disubstituted isoxaozolidines have thus been found to have a slight preference for the *trans*-invertomers [17]. The conformation of five-membered ring system is indeed very complex to elucidate with some certainty. The complexity arises from the fact that changing the size of the substituent may lead to change in conformation (half chair/envelope/near planar) and the flap of the envelope.

The dynamic cycle depicting the pseudorotation (Pr) and nitrogen inversion (Ni) in isoxazolidines is shown in Scheme 3.

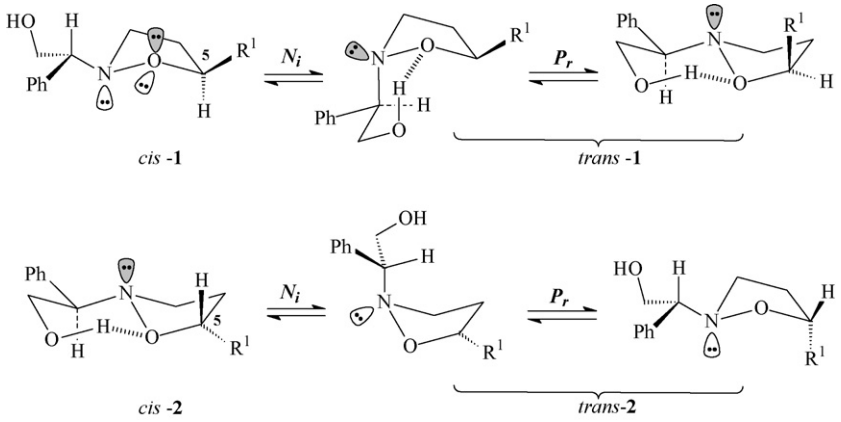


Scheme 3. Pseudororation (Pr) and nitrogen inversion (Ni) in isoxazolidines (2).

Even though III is depicted as pseudo diequatorially substituted, there will be considerable steric repulsion between the substituents since staggering in the heterocyclic five-membered ring is not as pronounced as in the six-membered systems. In fact actual conformations of the *trans* isomer would lie somewhere between I and II and that of the *cis*-invertomer between III and IV.

Earlier works [17,18] on 2,5-disubstituted isoxazolidines revealed the *trans*-invertomer as the major isomer. The 2-methyl-, 2-isopropyl- and 2-^{t}butyl-5-^{t}butyldimethylsiloxymethylisoxazolidines were found to have the *trans*- and *cis*-invertomers in a ratio of 53:47, 55:45 and 63:37, respectively. The compounds studied in this work are sterically similar to the 2-isopropylisoxazolidines since they also contain a secondary alkyl (i.e. phenylhydroxyethyl) substituent at the 2-position (Scheme 2). It is interesting to note that the isoxazolidines **1b**, **1d**–**1f** exist as a single invertomer in each case, and display sharp NMR signals at ambient as well as lower temperatures. However, all the isoxazolidines in the series **2**, revealed the presence of two invertomers at the lower temperatures. For instance, while the isoxazolidine **1b** exists as a single invertomer, the corresponding diastereomer **2b** shows the presence of two invertomers in a ratio 55:45, respectively. This is surprising since the *trans*-**1** and *trans*-**2** (or *cis*-**1** and *cis*-**2**) (Scheme 2) seem to have comparable steric environments, and as such a large difference in the population ratio of the invertomers in **1b** and **2b** demands an explanation as to the origin of such a descrepency. Similar trend is observed for the other isoxazolidines; while most of the isoxazolidines in series **1** remained exclusively as a single invertomer in each case, the compounds **2** show the presence of two invertomers. The analysis below will help us to explain the subtle differences in the stereochemistry between the isoxazolidines **1** and **2** and provide rationale for identifying the major invertomers as having *trans* configuration.

The likely configuration of the invertomers of the isoxazolidines is shown in Scheme 4. The Newman projections around the exocyclic C–N bond are shown in Scheme 5. Benzylic 'H'

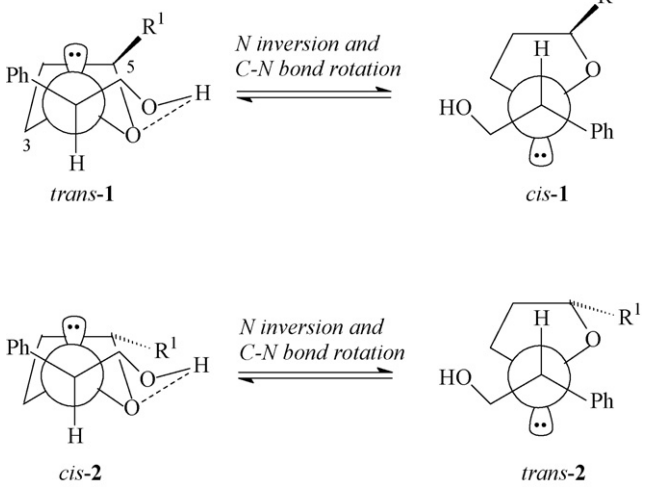


Scheme 4.

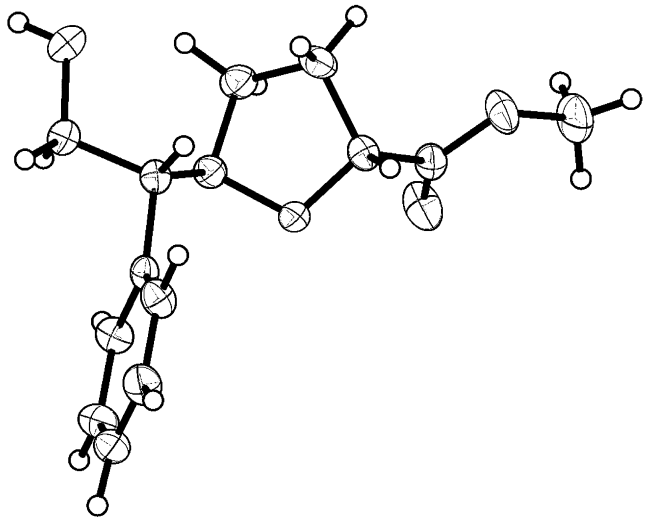
is placed *anti* to the nitrogen lone pair in all the projections since it will have the lower number of gauche interactions (two in these cases). Molecular models reveal that these conformations do not help the OH group make effective H-bonding with the nitrogen lone pair. The H-bonding in that case will be in a less favourable five-membered ring structure and will develop considerable eclipsing between the phenyl group and N–C(3) bond of the isoxazolidine ring. Moreover, the nitrogen in the isoxazolidine moiety is much less basic than in the ordinary amines (*vide infra*) due to the presence of the adjacent oxygen, and thus more reluctant to allow its lone pair to participate in an H-bond formation. This would leave the possibility of H-bonding with the ring oxygen in *trans*-**1** and *cis*-**2** invertomers as shown in Schemes 4 and 5. The *cis*-**1** and *trans*-**2** cannot form H-bonded structure. The *trans*-**1** has the two advantages – sterically favored *trans* disposition of the substituents as well as H-bonding – rendering it overwhelmingly favored over the *cis*-**1** and as such it exists as the sole invertomer. For the isoxazolidines **2**, each invertomer enjoys one advantage; while the *cis*-**2** is H-bonded, the *trans*-**2** enjoys the *trans* disposition of the substituents. As a result, both the invertomers exist for the isoxazolidines **2**.

To confirm the stereochemistry, adduct **2b** (the only crystalline compound among the isoxazolidines studied) was subjected to X-ray crystallographic analysis; the ORTEP representation is shown in Scheme 6. The isoxazolidine **2b** exists in $CDCl_3$ as two invertomers in a ratio of 55:45. Needless to say, the favourable invertomer in the solid state, as dictated by the crystal packing forces, may not be the conformation of choice in the solution. However, it was found that the isoxazolidine prefers to be in the *trans*-**2** invertomer in the solid as well as in solution. It can be seen that the *trans*-**2** invertomer is not intramolecularely H-bonded and benzylic 'H' is *anti* to the nitrogen lone pair as anticipated in Schemes 4 and 5. The relative stabilization imparted by the substituents in *trans* disposition in *trans*-**2**, and H-bonding in *cis*-**2**, dictate the population ratio of the isoxazolidines **2** and will vary depending on the size of the substuituent at C(5). As evident from Table 2, the CO_2Me substituent at C(5) in **2b** being smaller than the C(5) substituents in all the other isoxazolidines **2**, gave the highest percentage of the *cis*-**2** invertomer in $CDCl_3$.

The above discussion regarding H-bonding gets credence when the hydroxyl group in **1b** and **2b** is acetylated to give **1c** and **2c**, respectively. In the absence of H-bonding, the *trans*-**1b**



Scheme 5.



Scheme 6. ORTEP drawing of **2b**.

and *cis*-**1b** ratio of 100:∼0 is changed to 87:13 for the *trans*-**1c** and *cis*-**1c**, respectively, while the *trans*-**2b** and *cis*-**2b** ratio of 55:45 is changed to 70:30 for the *trans*-**2c** and *cis*-**2c**. As can be seen from Scheme 4, after acetylation the amount of *trans*-**1c** and *cis*-**2c** decreases in comparison to *trans*-**1b** and *cis*-**2b** owing to the absence of H-bonding.

Assignment of major invertomers to the *trans* conformers gets further credence by studying the population ratio in CD_3OD (Table 2). In methanol solvent, the nitrogen as well as oxygen lone pairs will be involved in H-bonding with the solvent. As such, in the absence of intramolecular H-bonding, the *trans*-**1** and *cis*-**2** will loose their advantages in favor of the *cis*-**1** and *trans*-**2**, respectively. This is exactly what is observed: while most of the *cis*-**1** invertomers are absent in $CDCl_3$, a considerable proportion exists in CD_3OD. However, for **2** in CD_3OD the results are mixed; while the population of *cis*-**2** is expected to decrease owing to the disruption of intramolecular H-bonding (Schemes 4 and 5), the solvation of the nitrogen lone pair will act in opposite way to increase its population. The overall effect on the population ratio would then depend on the relative importance of the two effects.

The chemical shift difference between the isomers for a particular ring carbon is generally less than 1 ppm for most carbons and as such the C-13 shifts are not very sensitive to the difference in the isomeric conformations (Table 1). This is not surprising in view of the fact that the five-membered ring does not have the well-defined conformation of six-membered systems. While the use of ^{1}H NMR coupling constant using the Karplus equation is highly successful in assigning configuration of six-membered rings, such applications often do not work well with isoxazolidines or any five-membered ring systems. For the isomers **1a** and **2a**, while the C-3, C-5 and N–C (external C attached to N) of the *trans*-invertomers appear at lower fields, the C-4 appears at slightly higher fields than the corresponding *cis* invertomers (Table 1). The N–C of the *cis*-invertomer absorbs upfield presumably due to the crowded environment of the carbon in a *cis* disposition with the C(5) substituents. Similar trends are observed in the compounds **2b** and **2d**. Such trends are not observed in the chemical shift values of **1c**, **2c** pair owing to the absence of H-bonding. Further evidence that the major isomer in the pairs **1e**, **2e** and **1f**, **2f** have the same configuration (i.e. *trans*) comes the similarity in the chemical shifts values within the pair.

It is well known that an axial proton in cyclohexane systems appears highfield than the equatorial proton. Further evidence that the major invertomers in all these isoxazolidines have the same *trans* configuration comes from the signal of C(5)H which, by virtue of being pseudo-equatorial in one of the *trans*-invertomer (Scheme 4), invariably appears downfield in comparison to the pseudoaxially disposed C(5)H in the *cis*-invertomers (Table 3). The C(5)H of the *trans*-**1**, in turn, appears downfield with respect to that of the corresponding *trans*-**2** invertomer; a diagnostic trend that would enable us to identify the stereochemistry of this important class of cycloaddition reactions.

The nitrogen inversion barrier is expected to be high when an oxygen atom is directly attached to the nitrogen as in isoxazolidines [11,19]. The inversion barriers hover around 60 kJ/mol

Table 3
^{1}H NMR chemical shifts of C(5)H signals of the compounds studied in $CDCl_3$ and CD_3OD at −30 °C

Isoxazolidine	δ (ppm)			
	$CDCl_3$		CD_3OD	
	Major-*trans*	Minor-*cis*	Major-*trans*	Minor-*cis*
1a	5.39	4.97	5.29	4.86
2a	5.16	4.72	5.03	4.83
1b	4.76	–[a]	4.78	4.35
2b	4.71	4.54	4.63	4.48
1c	4.79	4.50	4.80	4.42
2c	4.66	4.50	4.67	4.48
1d	4.52	–[a]	4.39	4.25
2d	4.34	–[b]	4.17	4.05
1e	4.46	–[a]	4.31	4.15
2e	4.29	–[b]	4.17	4.00
1f	4.56	–[a]	4.38	4.12
2f	4.29	–[b]	4.42	4.27

[a] No minor invertomer.
[b] Could not be detected as a result of very weak signal or overlapping with other signals.

for all the isoxazoldines. This is expected since the steric requirements to attain the sp^2 hybridized transition state (through which the nitrogen inversion occurs) remains more or less similar as the substituents in the immediate vicinity of nitrogen remains the same in all the isoxazolidines. The inversion barrier increases to some extent in hydrogen bonding solvent CD_3OD. Any increase in the barrier in cyclic system is attributed to the extra energy required for breaking of H-bonding prior to inversion [19]. The H-bonding involving the nitrogen lone pair may be minimal since the nitrogen in the isoxazolidine moiety is much less basic than in the ordinary amines (*cf.* pK_b of Me_3N (4.19) versus pK_b of Me_3N–OMe 10.35) [20]. The electron-withdrawing power of the oxygen reduces the electron-donating power of the nitrogen by a large amount. The presence of electronegative oxygen attached to the nitrogen results in more 's' character in the lone pair orbital and as such the nitrogen would form very weak H-bonds. A more effective intramolecular H-bonding to the ring oxygen in $CDCl_3$ or intermolecular H-bonding with CD_3OD could be achieved, however, in such a scenario there would be only minimal effect, if any, on the inversion barriers [21].

The NMR study at lower temperatures has thus led successfully the foundation using which the stereochemistry of this important class of chiral nitrone cycloaddition reactions might be determined.

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