The stereochemistry study of N,N-dinitrosopiperazine using $^1$H NMR technique

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Research Article

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Abstract

*N*-nitrosamines exist as two zwitter ions which are more stable than their neutral form. In the case of symmetric cyclo *N*-nitrosamines with two nitroso groups, various studies were done on products which derived from piperazine. In order to nitrosation of only one of the NH groups the reaction was proceeded with 1mmol of NaNO$_2$. It is observed that nitrosation on the both of the NH groups are done, unexpectedly and half of the piperazine are remained intact. In the presence of 2 mmol of NaNO$_2$ per 1mmol piperazine, the whole of piperazine convert to *N,N*-dinitrosopiperazine which exist in two cis- and trans-chair conformations. In the presence of 4 mmol of NaNO$_2$ per 1mmol piperazine, the whole of piperazine convert to *N,N*-dinitrosopiperazine which exist in four conformers of cis- and trans- forms of chair and boat conformations.

1. Introduction

A compound with a nitroso group (N = O) attached to the nitrogen of a secondary or tertiary amine, directly, known as *N*-nitrosamine. The human bodies are easily absorbed *N*-nitrosamines through the skin, respiratory and digestive system [5–8]. *N*-nitrosamines are very applicable in the various industries [9–14]. The N = O group can undergo the oxidation [15], reduction [16–19], rearrangement [20], photolysis [21], cyclization [22], denitrosation [23] and radical reactions [24,25]. When nitrite ions are exposed to the secondary or tertiary amines in human organs, *N*-nitrosamines are formed [35–37]. Secondary *N*-nitrosamines have carcinogen and mutagenic properties. The studies done on rodents have shown that organs suffering with cancer depends on the type of nitrosamine [38,39]. To date, variety reagents [40–52] have been used for the *N*-nitrosating reactions.

*N*-nitrosamines are existed as two zwitter ions which caused by mobility of electrons from amine nitrogen to oxygen (Scheme 1). This feature creates only one product from the symmetric secondary amines ($R_1 = R_2$) that two attached groups of both sides the nitrogen ($R_1$ and $R_2$) are diastereotopic. Asymmetric secondary amines ($R_1 \neq R_2$) exist in two $E$ and $Z$ isomeric forms. The more stable isomer is the form with less steric prevention to $-$O$^-$ [40].

In this work, in a typical procedure, a mixture of various amounts of NaNO$_2$ (1 mmol, 2 mmol and 4 mmol), piperazine (1 mmol) and wet-SiO$_2$ 50% (0.2 g) were condensed in the presence of nano-kaolin-SO$_3$H (0.015g) as a solid catalyst at room temperature under solvent-free conditions (Scheme 3). The stereochemistry of products was studied by using $^1$H NMR spectra of the products.

2. Experimental

Preparation of *N,N*-dinitrosopiperazine

Nano- kaolin-SO$_3$H was prepared by the method reported in our previous work [41]. A mixture of NaNO$_2$ (1mmol, 2mmol and 4mmol), piperazine (1mmol) and wet-SiO2 50% (0.2g) was grinding in a mortar in
the presence of nano-kaolin-SO$_3$H (0.015 g) as a solid catalyst for 5–15 minutes at room temperature in solvent-free conditions. After completion of the reaction, as monitored by TLC (EtOAc:petroleum ether 3:7), the reaction mixture was washed with chloroform (2·3ml) and the catalyst was separated by filtration. The pure product was obtained after evaporation of the solvent from the filtrate.

Specreoscopic data

N,N -dinitrosopiperazine (A mixture of chair conformers and intact piperazine): $\tilde{\nu}_{\text{max}}$ (KBr)/cm$^{-1}$: 2926 (-C-H), 1600 − 1400 (C = C and N = N), 1000–1350 (C = O and C-N). $^1$H NMR (CDCl$_3$, 400 MHz)/$\delta$ ppm: trans isomer (48%): $\delta_H$ = 4.46 (t, 4H, $^3J = 6$ Hz), 3.91 (t, 4H, $^3J = 6$ Hz). cis isomer (33%): $\delta_H$ = 4.47 (s, 4H), 3.88 (s, 4H), pierazine (19%): $\delta_H$ = 9.56 (bs, 2H), 3.31 (m, 8H).

N,N -dinitrosopiperazine (Chair conformers only): $\tilde{\nu}_{\text{max}}$ (KBr)/cm$^{-1}$: 2926 (-C-H), 1600 − 1400 (C = C and N = N), 1000–1350 (C = O and C-N). $^1$H NMR (CDCl$_3$, 400 MHz)/$\delta$ ppm: trans isomer (54%): $\delta_H$ = 4.4 (t, 4H, $^3J = 6$ Hz), 4.04 (t, 4H, $^3J = 6$ Hz). cis isomer (46%): $\delta_H$ = 4.56 (s, 4H), 3.81 (s, 4H).

N,N -dinitrosopiperazine (A mixture of chair and boat conformers): $\tilde{\nu}_{\text{max}}$ (KBr)/cm$^{-1}$: 2923 (-C-H), 1600 − 1400 (C = C and N = N), 1000–1350 (C = O and C-N). $^1$H NMR (CDCl$_3$, 400 MHz)/$\delta$ ppm: $\delta_H$ = 4.61 s, 4H), 4.56 (s, 4H), 4.40 (m, 8H), 4.04 (m, 8H), 3.83 s, 4H), 3.81 (s, 4H).

3. Results And Discussion

Reaction 1: The reaction of piperazine with 1 mmol of NaNO$_2$ led to the formation of N,N-dinitrosopiperazine only, as the main product (Scheme 3). 19% of the piperazine amount remained intact. As shown in Fig. 1, in addition to the peaks attributed to the N,N-dinitrosopiperazine, the peak related to the NH of piperazine is observed at 9.56 ppm. N,N-dinitrosopiperazine exists in 2 cis- and trns- chair conformers. The ratio of cis and trans is 33:48.

Incorporation of the N,N-dinitrosopiperazine spectrum: In each conformer, the protons of each CH$_2$ being equal through inversion. As shown in scheme 4, the blue protons split by the red and vic versa.

Reaction 2: The reaction of piperazine with 2 mmol of NaNO$_2$ led to the formation of N,N-dinitrosopiperazine as the only product and all the amine were consumed. Figure 2 shows the spectrum of this product. In this spectrum, four peaks are observed in ratio of 1:1:1:1. These peaks are related to two cis and trans structural forms of the product which are shown in scheme 4. As can be seen in this scheme, a pairs of singlet and a pairs of triplet are attributed to cis and trans conformers, respectively.

Reaction 3: The reaction of piperazine with 4 mmol of NaNO$_2$ led to the formation of N,N-dinitrosopiperazine as the only product but this product exist as 4 conformers (Scheme 5). Figure 3 shows the spectrum of this product. In this spectrum, four peaks with ratios of 1:1:1:1 are observed. It seems that the splitting of these signals to be singlet, quartet, quartet and singlet but this is not true.
There are 2 pairs of singlets which seem as two doublets and 2 pairs of triplets which seem as two quartets. These peaks are related to four structural forms of the product, cis and trans, chair and boat conformers.

**Conclusion**

In this work, the stereochemistry of \(N,N\)-dinitrosopiperazine was studied by incorporation of \(^1\text{H}\) NMR spectra. It is observed that nitrosation on the both of the NH groups are done, by adding 1mmol of NaNO\(_2\) to 1 mmol of piperazine. In the presence of 2 mmol of NaNO\(_2\), the whole of piperazine convert to \(N,N\)-dinitrosopiperazine which exist in two cis- and trans- chair conformations. Finally, in the presence of 4 mmol of NaNO\(_2\), the whole of piperazine convert to \(N,N\)-dinitrosopiperazine which exist in four conformers of cis- and trans- forms of chair and boat conformations.

**Declarations**

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**Availability of data and materials:** Data and materials are available.

**References**


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**Schemes**

Schemes 1 to 5 are available in the Supplemental Files section.

**Figures**

![Figure 1](image-url)
$^1$H NMR spectrum of the product of reaction 1

Figure 2

$^1$H NMR spectrum of the product of reaction 2
Figure 3

$^1$H NMR spectrum of the product of reaction 3

**Supplementary Files**

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