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Molecular geometry and optical activity of *N*-nitroso-2,2,6,6-tetramethylpiperidines generated by spontaneous crystallization and inclusion complexation with optically active diols

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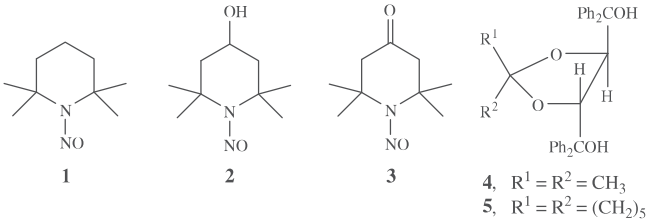
ABSTRACT

Three sterically strained *N*-nitrosamines and their inclusion complexes with optically active diols (TADDOLs) were obtained and their solid state crystal structures are described. Owing to the formation of *N*-nitroso-4-hydroxy-2,2,6,6-tetramethylpiperidine **2** as spontaneously resolvable conglomerate crystals (space group $P3_2$) its solid state CD was measured. The crystal structures of the inclusion complexes revealed that in all cases the guest nitrosamines assume chiral conformations as seen by their chiroptical spectra. The optically active nitrosamines are configurationally labile and rapidly racemize in solution. The solid state structures revealed that in order to avoid an allylic 1,3-strain [$A^{(1,3)}$], caused by an interaction of the nitrosamino group with the methyl substituents, the piperidine ring in **1** and **2** assumes a chair conformation significantly flattened at the amino nitrogen whereas in the 4-oxo derivative **3** the piperidine ring assumes a twist-boat conformation.

1. Introduction

N-Nitrosamines have attracted considerable interest over the past two decades since many compounds of this class are known to be potential carcinogens and mutagenic agents.[1] Since the molecular geometry and conformational properties critically influence the biological activity, the stereochemistry of *N*-nitrosamines has been the subject of many experimental and theoretical investigations.[2] In the case of piperidines a substitution of the nitrogen with an NO group strongly affects the conformation of the six-membered ring and the orientation of substituents. Due to so called allylic 1,3-strain [$A^{(1,3)}$][3,4] caused by an interaction of the planar *N*-nitrosamine system with the nearly coplanar equatorial substituents at C-2 and C-6 of *N*-nitroso-*cis*-2,6-dimethylpiperidine, this compound exists in solution almost exclusively in a diaxial conformation.[5] Similarly, its 2,6-diphenyl analogue prefers the sterically constrained diaxial conformation in the solid state as well as in solution, to relieve the more severe $A^{(1,3)}$ strain.[6]

However, in the case of *N*-nitroso-2,2,6,6-tetramethylpiperidine **1**, the $A^{(1,3)}$ strain cannot be avoided by inversion of the ring but instead the molecule may assume a non-chair conformation and/or increase a pyramidal character of the amino nitrogen. Continuing an interest in the stereochemistry and spectroscopy of *N*-nitrosamines,[4,7] we performed structural and spectroscopic studies on the sterically overcrowded compounds **1–3**.



1 **2** **3**

4, $R^1 = R^2 = CH_3$
5, $R^1 = R^2 = (CH_2)_5$

The introduction of the NO group at the nitrogen atom lowers the symmetry of the secondary amines and in the absence of any improper symmetry axis, *N*-nitrosamines **1–3** are chiral and may exist in two enantiomeric forms. Their chirality results from a hindered rotation about the partial double N–N bond and interconversion between the enantiomers may occur by rotation of the NO group or, as in case of **1** and **3**, by inversion of the six-membered ring. A chiral discrimination occurring during the complexation of *N*-nitrosamines with the optically active diols (*R,R*)-**4** and (*R,R*)-**5** allowed us to obtain the compounds **1–3** in the optically active forms and measure their solid state CD spectra. Furthermore, the 4-hydroxy derivative **2** crystallizes as a conglomerate that leads to spontaneous generation of chirality.[8]

2. Results and discussion

N-Nitrosamines **1–3** were prepared by nitrosation of the corresponding amines with HNO_2.

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