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On the Structure of *C,N*-Diphenylnitrone in 1,3-Dipolar Cycloaddition Reactions

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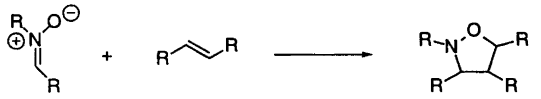
The geometry of *C,N*-diphenylnitrone, used in 1,3-dipolar cycloaddition reactions with alkenes, has been investigated using X-ray diffraction, NMR spectroscopy, and theoretical calculations. Based on these investigations it is confirmed that the nitrone has *Z*-geometry in the solid phase and in solution.

The 1,3-dipolar cycloaddition reaction [reaction (1)] of nitrones **1** with alkenes **2** giving isoxazolidines **3** is an important reaction in organic synthesis.[1] One of the challenges in recent years has been the development of methods for the preparation of optically active isoxazolidines.[2] Optically active isoxazolidines can be prepared either from optically active nitrones, optically active alkenes or by catalytic asymmetric synthesis.[2]



(1)

1 **2** **3**

Interest in catalytic 1,3-dipolar cycloaddition reactions of nitrones with alkenes has been focused on the control of regio-, diastereo- and enantio-selectivity,[2,3] and for these reactions, as well as the stereochemistry of the isoxazolidines formed, to be understood, knowledge of the substrate structure is necessary.

The nitrone geometry, which controls the relative configuration at C-3, C-4 in the product **3** obtained in these 1,3-dipolar cycloaddition reactions, has been the subject of some confusion. *C,N*-Diphenylnitrone **1a** can exist both as *Z*- and *E*-isomers, **1a**-*Z* and **1a**-*E*. It has been demonstrated that acyclic nitrones generally exist as the *Z*-isomer and that there is a large barrier to interconversion (20–30 kcal·mol^{-1}) of the *E*- and *Z*-forms.[4]

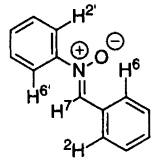
1a-*Z* **1a-*E***

However, in several recent papers concerning asymmetric 1,3-dipolar cycloaddition reactions of nitrones with alkenes it has been stated that *C,N*-diphenylnitrone **1a** is most stable in the *E*-geometry,[2a,3a,b,5] whereas based on the stereochemistry of the product we have claimed that **1a** reacts as the *Z*-isomer.[3d] In an attempt to resolve this confusion about the isomers of **1a**, this paper presents the results of X-ray diffraction and NMR spectroscopic investigations, and theoretical calculations on the geometry of *C,N*-diphenylnitrone **1a**.

Results and discussion

The X-ray structure of *C,N*-diphenylnitrone **1a** is shown in Fig. 1.[6] It shows that **1a** exists as the *Z*-isomer in the crystal. The bond lengths and bond angles of the nitrone part of **1a**, O9–N8 1.289(3) Å and N8–C7 1.297(4) Å, and ∠O9–N8–C7 124.4(2)°, ∠C1–C7–N8 126.5(3)° and ∠O9–N8–C1′ 116.0(2)°, are similar to those found for other nitrones characterized.[1b]

The ^{1}H NMR spectrum of *C,N*-diphenylnitrone **1a** has previously been described.[7] The ^{1}H NMR signal of the *ortho* protons of the *C*-phenyl group was found at very low field and this was mainly attributed to the direct effect of the negatively charged oxygen atom of the nitrone.[7] We have extended these NMR investigations with NOEDIFF and NOESY experiments, as we have investigated **1a** in ($^2H_6$)acetone in an attempt to study the geometric relationship between H^7 and $H^{2,6}$ and $H^{2',6'}$. Decoupling of H^7 in **1a** induces a positive NOE of 4.4% on $H^{2,6}$ and 4.4% on $H^{2',6'}$. These results strongly indicate that *C,N*-diphenylnitrone **1a** in a ($^2H_6$)acetone solution has *Z*-geometry, **1a**-*Z*.



1a-*Z*

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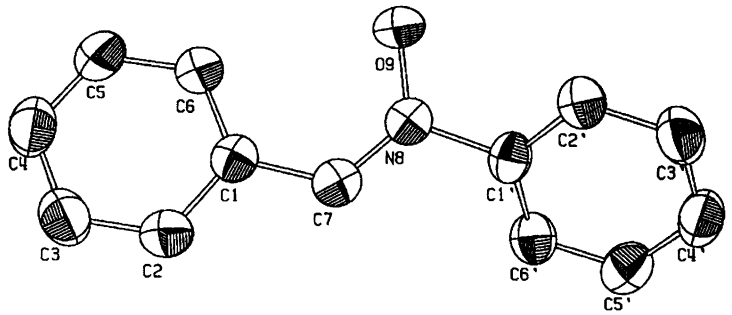

Fig. 1. The X-ray structure of *C,N*-diphenylnitrone **1a**.

The structure of *C,N*-diphenylnitrone **1a** has also been studied by theoretical calculations; the structure of **1a**-*Z* and **1a**-*E* and the transition state for their interconversion have been calculated using *ab initio* calculations.[8] The geometry of **1a**-*Z* and **1a**-*E* has been optimized using the 3–21G* basis set. The total energy for **1a**-*Z* and **1a**-*E* are calculated to be −624.412 and −624.396 au, respectively, showing that **1a**-*Z* is the most stable isomer by 11 kcal mol^{-1}. The bond lengths and bond angles of the nitrone part of **1a**-*Z* are calculated to be: O9–N8 1.38 Å and N8–C7 1.28 Å, and ∠O9–N8–C7 122.3°, ∠C1–C7–N8 127.5° and ∠O9–N8–C1′ 113.7°. These values are thus in agreement with those observed experimentally. The transition state energy for the interconversion of **1a**-*Z* to **1a**-*E* has been calculated to be 33 kcal mol^{-1}, showing that the interconversion of **1a**-*Z* to **1a**-*E* is not a very fast process at room temperature. The calculation of the total energies are for **1a**-*Z* and **1a**-*E* in a vacuum, in the absence of solvent, whereas the reaction of **1a** takes place in a solvent. In an attempt to compare the geometry obtained by the theoretical calculations with experimental results, the dipole moments for **1a**-*Z* and **1a**-*E* were calculated. The dipole moments for **1a**-*Z* and **1a**-*E* are calculated to be 3.98 and 5.69 D, respectively. The dipole moment of *C,N*-diphenylnitrone **1a** in benzene has been measured to be 3.44 D.[9] The dipole moment calculated for **1a**-*Z* in the gas phase is thus much more compatible with the experimentally observed value than the dipole moment calculated for **1a**-*E*.

The present experimental investigations and theoretical results for the structure of *C,N*-diphenyl nitrone **1a** strongly indicate that **1a**, both in the solid phase and in solution, has *Z*-geometry. It is therefore probable that **1a** also reacts in Lewis acid catalyzed 1,3-dipolar cycloaddition reactions with electron-deficient alkenes as the *Z*-isomer as the Lewis acid is coordinated to the alkene.

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