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Z/E CONFORMER ASSIGNMENTS. A METHYL GROUP AS PROBE FOR PROTON HOMONUCLEAR OVERHAUSER ENHANCEMENTS.

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Summary: Nuclear Overhauser enhancement difference techniques allow the use of CH_3-groups as n.O.e. probes exemplified by Z/E conformer assignments.

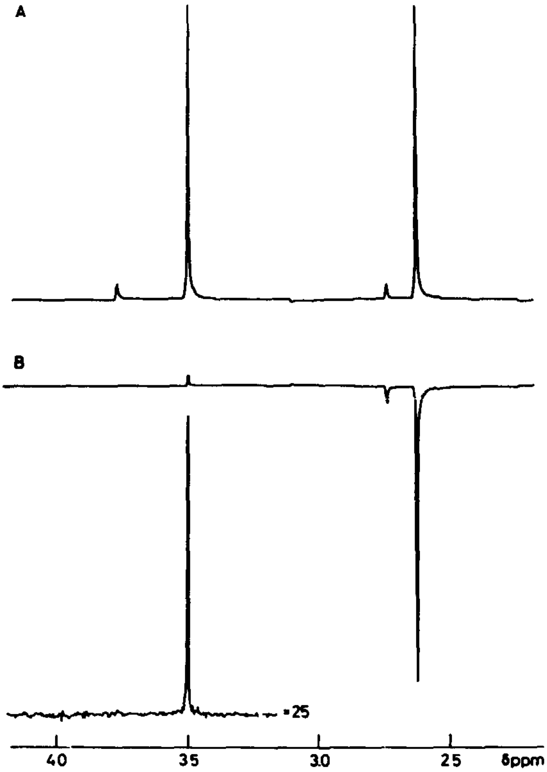
The use of nuclear Overhauser enhancement (n.O.e.) experiments for determining molecular structure and conformation is well established. However, the utility of the method is restricted by the fact that n.O.e. has not been observed for the protons of a methyl group.[1] Relaxation processes for methyl protons are completely dominated by intramethyl dipole-dipole and spin-rotation relaxation. Therefore an eventual Overhauser enhancement would be too small to be observed in a traditional n.O.e. experiment.[1]

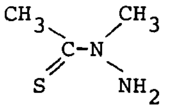
In this paper we report that $^1H-\{^1H\}$ Overhauser enhancements are in fact observable for methyl groups. Moreover, it is shown that these small enhancements, accurately measured by n.O.e. difference spectroscopy,[2] allow the use of CH_3-groups as n.O.e. probes. The potentialities of the approach are illustrated by Z/E conformer assignment of N-methylthioacethydrazide.

The 270 MHz ^1H n.m.r. spectrum, Figure 1A, of N-methylthioacethydrazide shows the compound in solution to exist as a mixture of unequal amounts (6:94) of E and Z conformers.

Figure 1B shows the $^1H-\{^1H\}$ n.O.e. difference spectrum of the same sample obtained as the difference between a spectrum recorded with and without n.O.e. The n.O.e. was built up by simultaneous presaturation of the $C-CH_3$ protons of <u>both</u> isomers by alternate irradiation of the resonances at 2.6 and 2.7 ppm. To minimize the effects of spectrometer instabilities, 4 scans with irradiation on and 4 scans with irradiation removed from these resonances were accumulated alternatively. The irradiation was gated on during a waiting time of $5 \cdot T_1$ sec (35 sec) prior to each scan. The Overhauser enhancements are obtained for each isomer using the corresponding irradiated inverted peak as reference. The observed enhancement is 4.4% (± 0.3%) for the larger $\dot{N}-CH_3$ proton signal, while no detectable enhancement (<1%) was registered for the minor $N-CH_3$ signal. Thus, the isomer present in larger amount can unambiguously be assigned to the structure with spatially proximate methyl groups, i.e. the Z isomer.

In a recent review[3] on evaluation of various methods for E/Z conformer assignments in tertiary amides (including thioamides) it was concluded that the only unambiguous method is the use of n.O.e. effects. In order to study amides other than formamides by this method, $-CD_2H$ labelled compounds had to be synthesized and utilized for the n.O.e. experiment. Assignments using arguments based upon coupling constants, chemical shifts, benzene dilution shifts, lanthanide induced shifts etc. often lead to conflicting results.[3] This was also found to be the case for N-methylthioacethydrazide chosen for the present study and stresses the potential usefulness of the approach outlined in this paper.

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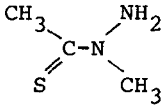
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Figure 1.
(A) 270 MHz FT ^1H n.m.r. spectrum at 30°C of N-methylthioacethydrazide (5% in $CDCl_3$). The NH_2-proton signal is not included.
(B) The analog $^1H-\{^1H\}$ n.O.e. difference spectrum. The upfield methyl groups of both isomers were simultaneously presaturated by alternate irradiation at 2.73 and 2.62 ppm.

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