Tetrahedron Letters No.51, pp. 5293-5297, 1968. Pergamon Press. Printed in Great Britain.

NITROGEN-15 MAGNETIC RESONANCE SPECTROSCOPY. II. CONFIGURATIONAL ASSIGNMENTS AND INTRAMOLECULAR HYDROGEN-BONDING IN N-NITROSOHYDRAZINES.

T. Axenrod and P. S. Pregosin
Department of Chemistry
The City College of The City University of New York
New York, N. Y. 10031

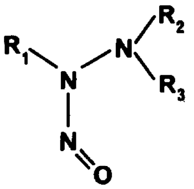
and

G. W. A. Milne
Laboratory of Metabolism
National Heart Institute
Bethesda, Md. 20014

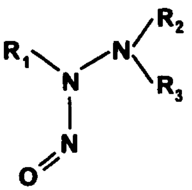
(Received in USA 10 July 1968; received in UK for publication 15 September 1968)

It is well established that N-nitrosoamines show restricted rotation about the N-N bond (1). Recently, we reported on nmr studies of N-nitrosamines using nitrogen-15 substitution in the nitroso group to make configurational assignments in these compounds (2). We would like now to report on the extension of these studies to the determination of configurations in the related N-nitrosohydrazine system.

As a class of compounds N-nitrosohydrazines have received relatively little systematic attention beyond the early preparative work of Thiele (3) and the more recent low-enrichment labeling studies concerned with the mechanism of nitrosation (4). While it is to be expected that these compounds would exhibit restricted rotation about the N-N=O bond due to appreciable $P_\pi - P_\pi$ bonding, this expectation has not been demonstrated. If π-bonding ($>\overset{+}{N}=N-O^-$) is important in these systems the presence of configurational isomers I and II should be discernible in their nmr spectra provided that the rate of interconversion is not extremely rapid or that the stability of one isomer does not greatly exceed that of the other. At the outset it was not clear whether steric factors as in nitrosamines(5,6) or other considerations would be important in determining the relative amounts of the two isomers present at equilibrium.



I



II

Configurational assignments in N-nitrosohydrazines have not previously been reported. Our earlier success in establishing configurations in the nitrosamine series based on the difference in the H-C-N-N^{15} coupling constants suggested that this method could be applied to the present investigation. Accordingly, a series of N-nitrosohydrazines were prepared and several of these compounds were labeled with nitrogen-15 (> 95% enrichment) in the nitroso group. Table I summarizes the chemical shift data for the protons alpha to both nitrogen atoms in each configuration and the relative amounts of the trans (I) and cis (II) isomers present at equilibrium in the several N-nitrosohydrazines.

TABLE I

Proton Chemical Shifts in Cis- and Trans- N-Nitrosohydrazines[a,b]

$R_1N(NO)NR_2R_3$			cis[c]			trans[c]			%[d]
R_1	R_2	R_3	R_1	R_2	R_3	R_1	R_2	R_3	trans/cis
CH_3	H	H				3.60	6.10	6.10	100/0
$PhCH_2$	H	H				5.22	5.70	5.70	100/0
$PhCH_2$	CH_3	H				5.20	2.50	2.50	100/0
$PhCH_2$	$PhCH_2$	H				5.14	3.84		100/0
CH_3	$PhCH_2$	H				3.55	3.90		100/0
$PhCH_2$	CH_3	CH_3	4.80	2.62	2.62	5.13	2.85	2.85	21/79
$PhCHCH_3$	CH_3	CH_3	5.42	2.45	2.45	6.01	2.63	2.63	41/59
CH_3	CH_3	CH_3	3.08	2.65	2.65	3.63	2.85	2.85	9/91

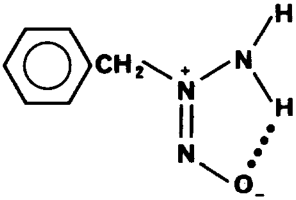
[a] Spectra were measured in $CDCl_3$ solution using either a Varian A-60 or HA-100 spectrometer. [b] The trans configuration is defined as the one having the nitroso-oxygen oriented syn to the adjacent amino-nitrogen atom. [c] Chemical shift values of the α -protons are reported in ppm relative to TMS as internal standard. [d] At magnet temperature, ~37°.

The interesting feature of these data is that the nitrosohydrazines may be divided into two groups; those in which either or both R_2 and R_3 are hydrogen, and those in which neither R_2 or R_3 are hydrogen. The nmr spectra of compounds in the former group show only a single set of resonances indicating the presence of only one configuration.[1] The spectra of compounds in the latter group which contain three alkyl substituents do indeed provide evidence for the presence of two configurational isomers. On heating, these compounds exhibit the typical temperature dependent coalescence sequence which can be attributed to an increased rate of rotation about the N-NO bond.

---

[1] A rapidly interconverting pair is not ruled out but is considered unlikely because the spectra remain essentially unchanged when the temperature is raised or lowered.

The conclusion to be reached in the case of mono- and dialkyl nitrosohydrazines is that the trans configuration is preferentially stabilized due to hydrogen-bonding as shown in III. The equilibrium thus favors the trans configuration in which intramolecular hydrogen bonding is possible. This conclusion is supported by further observations.



III

TABLE II

Coupling Constants in N-[^{15}N-Nitroso]-hydrazines.

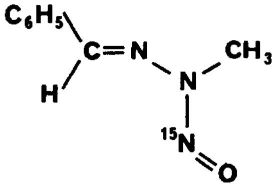
$R_1N(^{15}NO)NR_2R_3$			$J^a_{HCNN^{15}}$		J^a_{HNCH}
R_1	R_2	R_3	Cis	trans	
$PhCH_2$	H	H	-	2.2	
CH_3	$PhCH_2$	H	-	2.2	6.5
$PhCH_2$	$PhCH_2$	H	-	-	6.0[b]
$PhCH_2$	CH_3	H	-	2.2	6.0
$PhCH_2$	CH_3	CH_3	0	2.2	
$PhCHCH_3$	CH_3	CH_3	0	1.9	

[a] All coupling constants expressed cps. [b] Obtained from the unlabeled compound.

The coupling constant data presented in Table II clearly show a difference in the magnitude of the H-C-N-N^{15} coupling depending on the orientation of the nitroso group. By analogy with the coupling constants observed in ^{15}N labeled nitrosamines where it was shown that the trans H-C-N-N^{15} coupling was 2-3 cps and the cis coupling was approximately zero, we suggest that a similar situation exists in the case of N-nitrosohydrazines. In each of the examples studied where only one isomer is detected and hydrogen-bonding is presumably responsible it can be seen that the H-C-N-N^{15} coupling falls in the range 2-3 cps which is in agreement with earlier work (1). Furthermore, in those examples where R_1 = $PhCH_2$ the chemical shift values recorded in Table I for the benzyl protons fall in the range 5.13 - 5.22 ppm which is consistent with their being assigned as trans to the nitroso-oxygen. Cis- α-benzyl protons would appear at higher fields (4.7 ppm) due to the shielding effect of the nitrosamino group (6,7). In this connection it is noteworthy to point out, as Karabatsos (6) has done, that whereas trans- α-methyl and methylene protons resonate at lower fields than their cis counterparts, the reverse is true for α-methine protons. In view of the observation that only the high field quartet shows evidence of coupling to ^{15}N in 1-(α-phenylethyl)-2,2-dimethyl-N-nitrosohydrazine it would seem that similar conformational arguments apply to these systems.

Further evidence for the importance of hydrogen-bonding in these systems comes from the observation of H-N-C-H coupling reported in Table II. Ordinarily, rapid exchange between amino protons obscures observation of coupling between hydrogen on nitrogen and the adjoining protons on carbon in alkylhydrazines. Evidently, a strong hydrogen bond between the nitroso oxygen atom and the neighboring hydrogen bonded to nitrogen slows the rate of exchange of the latter so that H-N-C-H coupling of the order of 6-6.5 cps can readily be observed.

In the course of this work some preliminary data regarding the configuration of N-nitrosohydrazones were obtained. The nmr spectra of the N-nitroso derivatives of benzaldehyde methylhydrazone and benzaldehyde benzylhydrazone indicate the presence of only one configurational isomer in each case. From the observation that the methyl resonance in the ^{15}N-substituted compound IV appears as a singlet (δ 3.43), it is tentatively suggested that these compounds exist in the cis configuration shown below.



IV

Acknowledgments. - This work was supported in part by grants from The City College General Faculty Research Committee and The City University of New York. We are indebted to Mr. S. Liebgold for his assistance. One of us (T. A.) gratefully acknowledges the receipt of a Faculty Research Fellowship from the Graduate Division of The City University of New York.

References

(1) C.E. Looney, W.D. Phillips and E.L. Reilly, J. Am. Chem. Soc., 79, 6136 (1957).
(2) T. Axenrod, P.S. Pregosin and G.W.A. Milne, Chem. Commun., 12, 702 (1968).
(3) J. Thiele, Ann., 376, 239 (1910).
(4) K. Clusius and K. Schwarzenbach, Helv. Chim. Acta, 42, 739 (1959).
(5) H. W. Brown and D. P. Hollis, J. Mol. Spectrosc., 13, 305 (1964)
(6) G. J. Karabatsos and R. A. Taller, J. Am. Chem. Soc., 86, 4373 (1964).
(7) R. K. Harris and R. A. Spragg, J. Mol. Spectrosc., 23, 158 (1967).