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High Resolution ^{1}H NMR Studies of Cyclic *N*-Nitrosamines

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Molecular modeling by molecular mechanics (MM2) calculations were used to predict conformational preferences of cyclic *N*-nitrosamines. The results were compared with ^{1}H NMR data. The observed geminal coupling constants ^2J were considerably stronger for *syn* than for *anti* α-methylene protons and thus appear to be very useful for configurational predictions. The long-range ^4J couplings across the nitrogen atom were observed directly from the 1D spectra.

KEY WORDS NMR ^{1}H NMR Molecular modeling Cyclic *N*-Nitrosamines ^{1}H,^{1}H Spin–Spin coupling

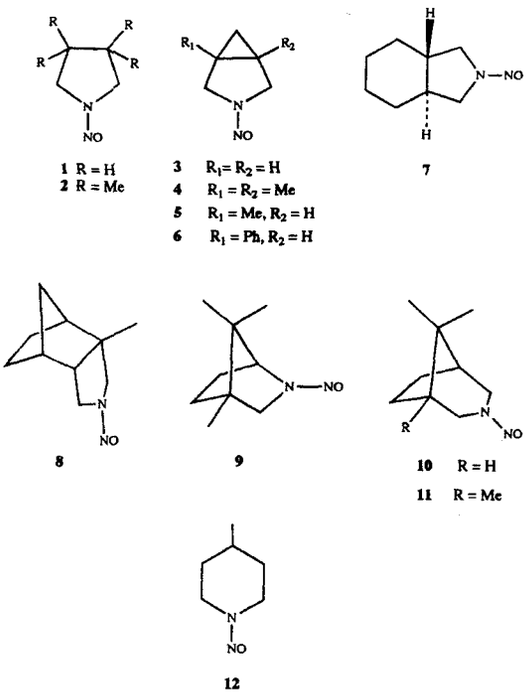
INTRODUCTION

N-Nitrosamines have been extensively investigated using ^{1}H NMR spectroscopy to determine their stereochemistry[1,2] and barriers to N—N rotation.[2,3] Because rotation around the N—N bond is slow on the NMR time scale, it is possible to observe signals corresponding to configurational isomers. A magnetic anisotropy of the nitrosamino group gives rise to the different chemical shifts of the protons being *syn* and *anti* to the nitroso oxygen. Shielding and deshielding zones of the NNO group have been proposed to facilitate stereochemical assignments.[4]

Most of the work on this class of compounds has been confined to acyclic or flexible molecules, where conformationally averaged parameters have been measured. Recently, we have prepared and studied chiroptical spectra of some bi- and tricyclic *N*-nitrosamines of rigid structures or very limited conformational mobility.[5] This paper reports the ^{1}H NMR examination of compounds **1–12**; besides chiral molecules obtained earlier, we synthesized and studied some symmetric model compounds including, for comparison, flexible compounds **1** and **2**. We were interested in the correlation of the molecular modeling of their geometries with the NMR parameters characterizing those structures. We were also able to observe, for the first time, long range ^{1}H–^{1}H couplings ^4J across the nitrosamino nitrogen. The appropriately substituted compounds **2** and **4** helped to demonstrate these couplings unequivocally.

RESULTS AND DISCUSSION

^{1}H NMR data of *N*-nitrosamines **1–12** are summarized in Table 1. The geometries of the energy minimum conformations were calculated by the molecular mechanics method. The original Allinger's MM2 force field[6] was extended with some additional parameters involving the NNO functional group.[5] Selected torsional angles are in Table 2.



The five-membered ring in *N*-nitrosopyrrolidines adopts a half-chair (twisted) conformation as shown by MM2 calculation and confirmed by the X-ray determined crystallographic structure.[5] Owing to a rapid interconversion between two equivalent half-chair conformers four α-methylene protons in **1** and **2** give rise to only two signals in the ^{1}H NMR spectrum. In **7** the twisted conformation of the pyrrolidine ring is locked by the *trans*-fused six-membered ring. The bi- and tricyclic skeletons in the remaining compounds reduce or rule out their conformational flexibility. The 3-azabicyclo[3.1.0]hexane skeleton in **3–6** assumes a boat-like conformation in solution:

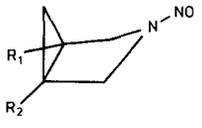


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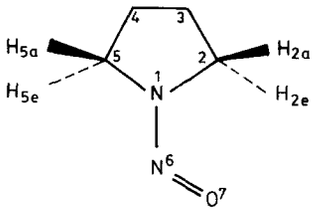
Table 1. ^{1}H NMR data of *N*-nitrosamines[a]

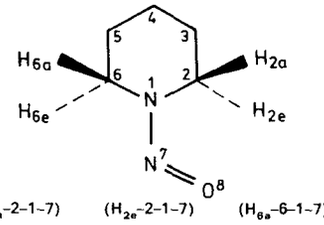
Compound	Solvent	*syn*-C_5H_2 δ_e[b]	*syn*-C_5H_2 δ_a[b]	*anti*-C_5H_2 δ_e[b]	*anti*-C_5H_2 δ_a[b]	$^2J_{syn}$	$^2J_{anti}$	^4J[c]
1	$CDCl_3$	3.51		4.21		—	—	1.2
2	$CDCl_3$	3.43		4.12		—	—	1.2
	C_6D_6	3.22		3.64		—	—	1.1
3	$CDCl_3$	4.08	3.39	4.50	4.31	14.3	12.1	1.3[d]
4	$CDCl_3$	4.17	3.10	4.55	4.07	14.1	11.9	1.3[d]
	C_6D_6	4.01	2.67	4.09	3.37	13.8	11.6	1.3[d]
(*Z*)-**5**	$CDCl_3$	4.16	3.17	4.50	4.36	14.1	12.2	1.4[d]
(*E*)-**5**	$CDCl_3$	4.08	3.43	4.56	4.11	14.1	12.1	1.3[d]
(*Z*)-**5**	C_6D_6	3.92	2.72	4.01	3.70	13.8	11.6	1.4[d]
(*E*)-**5**	C_6D_6	3.84	2.93	4.07	3.48	13.9	11.7	1.3[d]
(*Z*)-**6**	$CDCl_3$	4.54	3.59	4.68	4.50	13.9	12.1	1.4[d]
(*E*)-**6**	$CDCl_3$	4.29	3.54	4.91	4.53	14.1	11.9	1.3[d]
(*Z*)-**6**	C_6D_6	4.33	3.15	4.07	3.62	13.7	11.7	1.3[d]
(*E*)-**6**	C_6D_6	3.99	2.89	4.39	3.87	13.8	11.7	1.3[d]
7	$CDCl_3$	3.86	2.91	4.51	3.60	14.2	11.2	1.9, 0.8
	C_6D_6	3.58	2.61	4.04	3.00	13.9	10.9	1.9, 0.8
(*Z*)-**8**	$CDCl_3$	4.48	2.64	4.54	4.04	15.1	13.3	1.8, 1.4
(*E*)-**8**	$CDCl_3$	4.29	3.06	4.71	3.60	15.0	13.3	1.9, 1.4
(*Z*)-**8**	C_6D_6	4.36	2.14	4.12	3.31	14.8	13.2	1.9, 1.4
(*E*)-**8**	C_6D_6	4.17	2.49	4.28	2.95	14.9	13.1	1.9, 1.4
(*Z*)-**9**	$CDCl_3$	3.28	3.06	—	4.49	13.8	—	0.7
(*E*)-**9**	$CDCl_3$	3.93	3.77	—	4.55	—	11.1	0.7
10	$CDCl_3$	4.50	2.94	4.43	4.12	14.6	13.2	x
	C_6D_6	4.48	2.47	4.13	3.54	14.4	13.1	x
(*Z*)-**11**	$CDCl_3$	4.34	2.68	4.43	4.13	14.5	13.2	1.6, 0.9
(*E*)-**11**	$CDCl_3$	4.54	2.95	4.22	3.84	14.4	13.2	1.6, 0.9
(*Z*)-**11**	C_6D_6	4.34	2.27	4.16	3.56	14.4	13.1	x
(*E*)-**11**	C_6D_6	4.50	2.48	3.97	3.34	14.4	13.1	x
12	$CDCl_3$	4.97	2.54	4.69	3.64	13.3	13.3	1.8, 0.95

[a] Chemical shifts (δ) in ppm, coupling constants J in Hz.
[b] e = equatorial; a = axial.
[c] x denotes a cross-peak detected in the COSY contour plot.
[d] Additional couplings $^4J_{2,4} = {}^4J_{4,6} = 1.4$ Hz were observed.

Table 2. Selected torsional angles calculated by MM2 (only partial structures are shown)



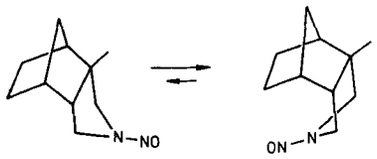
Compound	(2-3-4-5)	(1-2-3-4)	(H_{2a}-2-1-6)	(H_{2e}-2-1-6)	(H_{5a}-5-1-6)	(H_{5e}-5-1-6)
1	−41.1	31.4	−73.3	49.4	−78.6	43.7
2	−38.4	29.4	−70.1	49.9	−77.7	42.0
3	0.3	12.4	−86.7	37.0	86.8	−36.3
4	0.2	13.2	−87.9	35.9	88.1	−35.2
5	0.6	12.4	−87.1	36.6	87.3	−36.1
6	1.4	11.7	−86.9	36.7	87.1	−36.4
7	−45.5	35.0	−74.4	48.6	−79.6	43.0
8	2.8	−20.6	96.9	−24.7	−94.4	24.8
9	−56.0	36.4	59.2	−63.5	—	21.0



	(1-2-3-4)	(H_{2a}-2-1-7)	(H_{2e}-2-1-7)	(H_{6a}-6-1-7)	(H_{6e}-6-1-7)
10	−55.7	93.8	−23.0	−94.2	22.1
11	−56.2	94.2	−22.8	−94.2	21.3
12	−53.1	115.9	−2.3	−115.5	2.5

This type of geometry is characteristic for the parent bicyclo[3.1.0]-hexane molecule, and its 3-aza and 3-oxa analogues as shown by electron or X-ray diffraction structures.[7] The vicinal coupling constants $^3J_{\alpha\beta}$ between α and β protons were calculated by the equation of Gandour and co-workers[8] on the basis of corresponding dihedral angles obtained from the MM2 method. Calculations for compounds **3**, **5** and **6** gave values of 4.4 and 1.3 Hz in agreement with observed values 4.5 and 1.2 Hz.

Molecular modeling predicts two energy minima for the tricyclic molecule **8**; in both, the pyrrolidine ring assumes an envelope conformation (the nitrogen atom at the tip). However, the calculated steric energy for the *exo* form is around 3 kcal mol^{-1} higher than for the *endo* form. Thus the conformational equilibrium must be shifted completely towards the latter form. The calculated $^3J_{\alpha\beta}$ values for the *endo* conformer, 7.2 and 2.3 Hz, are close to observed values of 8.8 and 1.6 Hz, whereas for the *exo* form the values 10.9 and 10.4 Hz would be expected.



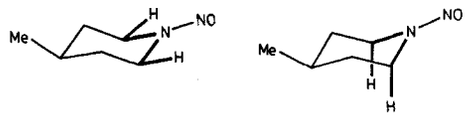
exo - 8 endo - 8

The piperidine ring in **10–12** has been shown to occur in a chair conformation.[4b,c] However, the MM2 calculations reveal that the six-membered ring in the bicyclic structures **10** and **11** is slightly distorted from a regular chair; puckering is decreased in the area of nitrogen and increased at the C-8.

The influence of the shielding effect of the nitrosamino group on differently oriented vicinal protons is illustrated by wide scattering (over 2 ppm for **10–12**) of the α-hydrogen signals in the spectra. The data show that even a small difference in torsional angles involving these atoms significantly affects their chemical shifts (e.g. **7** and **9**). It is known that the proton *syn* to the nitroso oxygen, which is nearly coplanar with the NNO group, resonates at lower frequency than the one *anti* to the oxygen.[4,9] The out-of-plane *syn* protons, however, are shielded relative to *anti* ones. Generally, the equatorial or pseudoequatorial hydrogens are further downfield from the corresponding axial or pseudoaxial ones located deeper in the shielding zone of the NNO group.

Because in conformationally restricted or rigid compounds all α-protons are located in different magnetic environments, four signals corresponding to these hydrogens are observed for each *Z* and *E* stereoisomer. A complete assignment of *syn* and *anti* protons based solely on shielding properties of the NNO group may cause some problems, especially in the case of an equilibrium mixture of *Z* and *E* configurational isomers. Inspection of the data in Table 1 shows that differences in chemical shifts of some hydrogens are very small and, moreover, the solvent changes may alter the sequence of the signals. It has been shown that *anti* protons exhibit a larger upfield shift over the *syn* ones, when the solvent is changed from CCl_4 or $CDCl_3$ to C_6D_6.[9] However, our data reveal that $\Delta\delta = \delta(CDCl_3) - \delta(C_6D_6)$ is indeed more positive for equatorial or pseudoequatorial *anti* protons, but axial or pseudoaxial *anti* protons do not necessarily show preferential upfield shift in C_6D_6 (e.g. **10** and **11**). Sometimes a consideration of steric effects facilitates configurational assignments,[9,10] e.g. in the case of **10** the nonbonded interaction of H-1 with the nearly coplanar nitroso oxygen effectively disfavours the *E* stereoisomer, hence the *E*/*Z* ratio is of 0.10. However in the absence of such interactions the *E*/*Z* ratio is close to 1 for remaining nitrosamines. For this reason assignments for more problematic cases were based on the COSY or spin decoupling experiments. The analysis of the spectra led us to the conclusion that the geminal coupling constant ^2J is substantially larger for *syn* than for *anti* α-methylene protons in **1–11**. The difference ranges from about 3 Hz for **7**, through 2 Hz for the majority of compounds, to around 1 Hz for **10** and **11**. An exception is *N*-nitroso-4-methyl-piperidine (**12**) showing the same ^2J couplings (13.3 Hz) for both methylene groups. The observed difference in ^2J values may serve as a valuable diagnostic tool for configurational assignments. It very probably arises from an interaction of the oxygen 2p component of the π NNO molecular orbital with the neighbouring *syn* methylene hydrogens: similar effects take place in other compounds with the methylene group adjacent to the π bond.[11] In our case this interaction is most effective for α-hydrogens symmetrically disposed in relation to the NNO plane (i.e. when both HCNN dihedral angles show comparable absolute values e.g. in **9**) and is very weak when the corresponding angles are very different (e.g. for axial and equatorial protons in **12**).

The complex structure of the multiplets corresponding to α-protons in some spectra (Figs 1 and 2) may suggest the occurrence of long-range couplings $^4J_{ee}$ and $^4J_{aa}$:



$^4J_{ee}$ $^4J_{aa}$

Such interactions across the sp^2 hybridized nitrogen have been proposed by Harris and co-workers[2] as a possible source of line broadening in the ^{1}H NMR spectra of *N*-nitrosamines but have never been observed directly. They are strong enough to be evidenced by the cross-peaks in the COSY spectra and are unequivocally manifested in the 1D spectrum of **2** as two well-resolved triplets at 3.43 and 4.12 ppm. These couplings can also be directly observed in the 1D spectra of the remaining compounds though sometimes the multiplets are obscured by additional ^4J couplings due to W paths between 2,4-H and 4,6-H in **3–6** and 2,7-H and 4,6-H in **10** and **11**. In some cases double irradiation helps to extract the ^4J coupling constants but in other cases the exact values are difficult to obtain.

Two kinds of ^4J couplings are observed in compound **12**; a stronger $^4J_{ee} = 1.8$ Hz and a weaker $^4J_{aa} = 0.95$ Hz, seeming to give a good illustration of the σ and π contributions to the long-range interaction[12] through the W arrangement of bonds and the π_{NNO} system, respectively. There is a lack of observable $^4J_{ae}$ values.

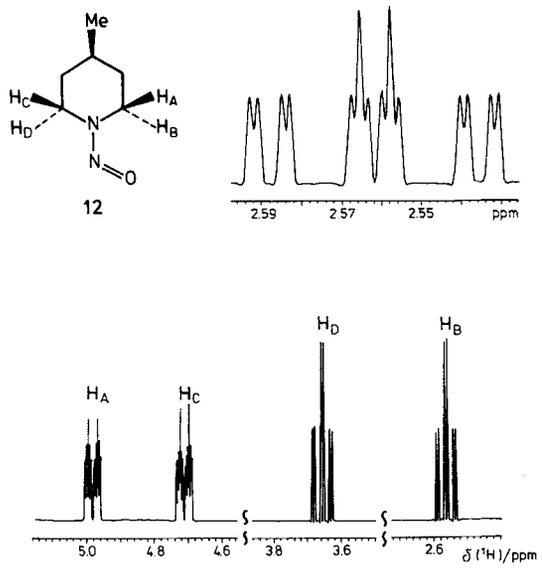


Figure 1. α-Methylene region of the 500 MHz ^{1}H NMR spectrum of **12**.

This behaviour of **12** closely resembles that of stereochemically related cyclohexanones.[12,13] Separation of the σ and π contributions is not possible for the remaining compounds, since the α-hydrogens do not occupy exactly equatorial or axial positions but pseudoaxial and pseudoequatorial ones as shown by the corresponding torsional angles. Analysis of the spectra of rigid compounds **7** (Fig. 2), **8** and **11** revealed that the strongest ^4J coupling (1.9 Hz in **7** and **8** and 1.6 Hz in **11**) occurs between two *cis* or *trans* pseudoaxially oriented hydrogens. The coupling between pseudoaxial and pseudoequatorial hydrogens is weaker (respectively 1.4 and 0.9 Hz) and between the two pseudoequatorial ones usually appears only as a line broadening. Nitrosamine **7** appears to be the exception, showing nearly

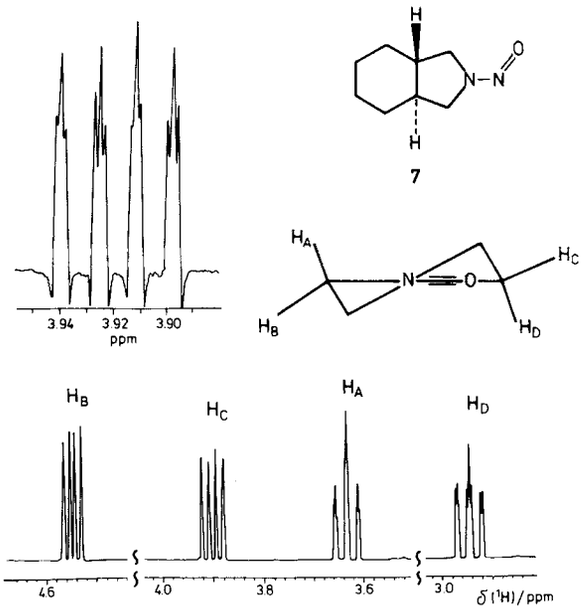


Figure 2. α-Methylene region of the 500 MHz ^{1}H NMR spectrum of **7**.

the same values for $^4J_{ae}$ and $^4J_{ee}$ of 0.8 Hz (Fig. 2). Thus the ^4J measurements may have some significance for the conformational analysis. Only one ^4J value (*ca.* 1.3 Hz) was observed for flexible rings in **1** and **2**. The absence of measurable long-range couplings in acyclic *N*-nitrosamines points to a possible contribution from the 'dual-path' mechanism[14] to the above interactions especially in the five-membered ring compounds.

EXPERIMENTAL

Spectra

The 1D and 2D NMR spectra were recorded using a Bruker MSL-300 and AM-500 spectrometers operating at 300 and 500 MHz, respectively. The deuteriated solvents were used as an internal lock. Spectra were recorded at room temperature in 5 mm tubes. Standard Bruker DISNMR software was used for processing the data. The digital resolution was 0.168 Hz per point. The preparation of compounds **5**, **6**, **8** and **10–12** was described earlier[4,5,15,16] and the nitrosamines **7** and **9** will be published elsewhere.

Compounds

3,3,4,4,-Tetramethylpyrrolidine was obtained by $LiAlH_4$ reduction of 2,2,3,3-tetramethylsuccinimide; hydrochloride m.p. 234–236 °C; ^{1}H NMR ($CDCl_3$) δ 9.71 (br s, 2 H, $^+NH_2$), 3.12 (t, 4 H), 0.98 (s, 12 H); ^{13}C NMR ($CDCl_3$) δ 55.75, 42.73, 21.96. Analysis calculated for $C_8H_{18}NCl$: C 58.70, H 11.80, N 8.56%; found: C 58.72, H 11.96, N 8.77%.

N-Nitroso-3,3,4,4-tetramethylpyrrolidine (**2**) was obtained by nitrosation of the above amine with HNO_2; after sublimation m.p. 121–124 °C. Analysis calculated for $C_8H_{16}N_2O$: C 61.51, H 10.32, N 17.93%; found: C 61.80, H 10.31, N 18.05%.

3-Azabicyclo[3.1.0]hexane was obtained by $LiAlH_4$ reduction of 1,2-cyclopropanedicarboximide; hydrochloride m.p. 162–164 °C; ^{1}H NMR ($CDCl_3$) δ 9.85 (br s, 1 H, ^+NH), 9.36 (br s, 1 H, ^+NH), 3.37 (m, 4 H), 1.65 (m, 1 H), 0.83 (m, 1 H), 0.75 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 47.08, 15.28, 7.00. Analysis calculated for $C_5H_{10}NCl$: C 50.22, H 10.09, N 11.71%; found: C 50.11, H 10.21, N 11.62%

N-Nitroso-3-azabicyclo[3.1.0]hexane (**3**) was obtained by nitrosation of the above amine with HNO_2 as an oil; ^{13}C NMR ($CDCl_3$) δ 52.36, 47.58, 29.64, 13.42, 12.94.

1,5-Dimethyl-3-azabicyclo[3.1.0]hexane was obtained by reduction of 1,2-dimethyl-1,2-cyclopropanedicarboximide with Red-Al (Aldrich) in toluene; hydrochloride m.p. 178–180 °C; ^{1}H NMR ($CDCl_3$) δ 9.80 (br s, 1 H, ^+NH), 9.31 (br s, 1 H, ^+NH), 3.40 (m, 2 H), 3.14 (m, 2 H), 1.16 (s, 6 H), 1.14 (m, 1 H), 0.35 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 51.99, 25.52, 18.80, 14.15. Analysis calculated for $C_7H_{14}NCl$: C 56.94, H 9.56, N 9.49%; found: C 56.66, H 9.91, N 9.67%.

N-Nitroso-1,5-dimethyl-3-azabicyclo[3.1.0]hexane (**4**) was obtained by nitrosation of the above amine with HNO_2; m.p. 28 °C (pentane); ^{13}C NMR ($CDCl_3$) δ 57.79, 52.76, 23.90, 23.50, 21.90, 14.68, 14.63.

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