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OXYGEN-17 NMR OF SELECTED *N*-NITROSAMINES. A PRELIMINARY REPORT

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Oxygen-17 NMR spectra of some *N*-nitrosamines are discussed in terms of steric and conjugative effects. Relationships have been observed between rotational barriers, conformations and ^{17}O chemical shifts. A tentative linear correlation has been determined between repulsive Van der Waals interactions and some *N*-nitrosopiperidines.

INTRODUCTION

N-Nitroso compounds have been widely studied[1] because of their biological activity as potential carcinogens. Despite many investigations, whether there is a relationship between the molecular structure of *N*-nitroso compounds and their activity is still an open question.[1]

Oxygen-17 NMR spectra are sensitive to steric perturbations[2] and electronic distribution[3] and should give results that can be compared with previous results based on, e.g., dynamic NMR[4,5] and ^{1}H, ^{13}C and ^{15}N NMR.[6,7] However, although numerous organic compounds have already been investigated by this technique, only two *N*-nitrosamines, the dimethyl[8] and diethyl[9] derivative, have been reported. In this work, the ^{17}O NMR of nine *N*-nitrosamines was studied.

RESULTS AND DISCUSSION

The structures of the compounds investigated are shown in Table 1 together with ^{17}O chemical shifts and measured line widths.

The first noteworthy observation is the great change in chemical shifts on going from aliphatic to aromatic *N*-nitrosamines. The chemical shift difference ($\Delta\delta$) between **1** and **9** is 55 ppm compared with only 26 ppm between *N*, *N*-dimethylformamide[9] and *N*-methyl-*N*-phenylacetamide.[10] This difference cannot be attributed to the presence of a mixture of two conformers, as **9** is known[11] to exist only in the conformation with the methyl group *cis* to the oxygen atom. The analogous amide[12] exhibits a similar conformation. On the other hand, Boykin *et al.*[10] demonstrated by ^{17}O NMR spectroscopy and molecular mechanics calculations a torsion angle of 62° between the carbonyl group and phenyl planes for *N*-methyl-*N*-phenylacetamide. Our MM2 calculations[13] on **9** yield a value of 23° between the nitroso group and phenyl planes, in good agreement with a microwave determination.[14]

The importance of conjugative effects between the amine-type nitrogen atom and phenyl ring(s) in aromatic *N*-nitrosamines has already been demonstrated by Forlani *et al.*,[5] who thus explained their findings that **7** and **8** have a lower rotational barrier than aliphatic *N*-nitrosamines.

A further proof of the sensitivity of *N*-nitrosamines to conjugative effects, as reflected by their ^{17}O NMR spectra, is obtained comparing **9** with **7** and **8**. Compound **7** has a further downfield difference of 26 ppm, due to the second phenyl ring, which does not have as much influence as the first because in **7** the two phenyl rings have two different torsion angles, namely 30° and 47° (MM2 calculations). Moreover, the lone pair on the nitrogen atom must be shared between two phenyl rings. MM2 calculations on **8**, owing to the rigidity of the carbazole system, yield a torsion angle near 0°. The downfield shift noted on comparison of **8** and **7** is 67 ppm, again in agreement with the lower rotational barrier[5] of **8** compared with **7**.

If we compare the ^{17}O NMR results with the ^{15}N results[7] (Table 2), we note that ^{15}N shifts seem to be determined mostly by steric factors for both N-1 and N-2 as shown by the $\Delta\delta$ values between **1** and **3** and between **1** and **7**, whereas a strong influence of electronic factors is shown on ^{17}O shifts. The lack of steric influence on ^{17}O shifts on going from **1** to **3** can be explained by considering that for **3** the preferred conformation[15] is that with the methynic hydrogen 'near' the oxygen atom, so causing only slight modifications compared with **1** and **2**. Interactions between the two alkyl groups are, on the other hand, unlikely to affect the O atom, from which they are far apart.

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Table 1. Oxygen-17 NMR data for *N*-nitrosamines

R_2NNO	R_2N	^{17}O (ppm)[a]	$\nu_{1/2}$ (Hz)
1	Dimethylamino	672	117
2	Diethylamino	669	196
3	Diisopropylamino	674	225
4	Piperidyl	660	205
5	2,6-Dimethylpiperidyl	669	295
6	2,2,6,6-Tetramethylpiperidyl	736	315
7	Diphenyl	753	800
8	Carbazolyl	820	600
9	Phenylmethyl	727	387

[a] As defined under Experimental.

Table 2. Chemical shifts differences for ^{15}N and ^{17}O.

Compound	$\Delta\delta$N-1 (ppm)	$\Delta\delta$N-2 (ppm)	$\Delta\delta$O (ppm)
1	0	0	0
2	−24·4	+2·3	−3
3	−39·5	+9·7	+2
9	−18·9	+9	+55
7	−36·9	+9·6	+81

On the other hand, steric influences on the ^{17}O NMR shifts are well established[16] and they ought to be detectable in systems where conformations such as that discussed for **3** are not possible.

Compounds **4**, **5** and **6** matched this requirement. The nitroso group is known to be coplanar with the medium plane of the ring,[4] as confirmed also by MM2 calculations, which for all of them gave torsional angles ranging from 22° to 27°. On the other hand, whereas **4** and **5** gave ^{17}O NMR chemical shifts similar to those for the alicyclic analogues, for **6** a 76 ppm deshielding is measured, which appears to be the largest compressional effect observed so far. If we assume that the electronic effect of substituting the protons at C-2 and C-6 with methyl groups is negligible, as is apparent from the ^{17}O NMR shifts for **1**–**3**, we can attribute the deshielding observed for **6** to important repulsive Van der Waals interactions.[16] In fact, if we compare the differences in MM2-estimated Van der Waals energies with the $\Delta\delta$ values for **4**, and **5** and **6**, we obtain a linear relationship $\Delta\delta = 28.99\Delta$ (Van der Waals) -2.59 ($r = 0.997$), which, being well aware of the fact that only three points have been used, could be a starting point to ascertain if for the *N*-nitroso group a correlation similar to that already developed for the carbonyl group[16] holds. Further spectroscopic studies on *N*-nitrosamines are in progress.

EXPERIMENTAL

Compounds. All the *N*-nitrosamines employed are known and were prepared by standard methods.[4]

NMR measurements. Oxygen-17 NMR spectra were acquired at 40.662 MHz using a Varian VXR-300 spectrometer, equipped with a 10-mm broad-band probe. All spectra were acquired at natural isotopic abundance at room temperature (probe temperature = 21°C) in spectroscopic-grade acetonitrile containing a few drops of acetone as an internal standard. The signals were referenced to external deionized water at room temperature. The acetone resonance (567 ± 1 ppm) was used as an internal check on the chemical shift measurements for the compounds studied. The concentration varied typically in the range 2–5 mol dm^{-3}, but in few cases (**2** and **4**) spectra were run at various concentrations (12–0.5 mol dm^{-3}) without notable changes in their chemical shifts. A saturated solution (0.4 mol dm^{-3}) was used for **8**.

Typical spectroscopic parameters were: pulse length 28 ms (*ca* 90°), pre-acquisition delay 100 μs, acquisition time 10 ms, spectral width 36 kHz, 740 data points and 15 000–60 000 scans. The spectra were recorded with sample spinning and without lock and decoupling. The signal-to-noise ratio was improved by applying a 30-Hz exponential broadening factor to the FID prior to Fourier transformation. The data point resolution was improved to 0·08 ppm by zero filling to 16K data points. The reproducibility of the chemical shifts data is estimated to be ±1·0 ppm.

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