Natural Abundance ^{17}O NMR Spectroscopy of Heterocyclic *N*-Oxides and Di *N*-Oxides. Structural Effects

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The ^{17}O chemical shift data for a series of azine *N*-oxides, diazine *N*-oxides and di-*N*-oxides at natural abundance are reported. Isomeric methyl substituted quinoline *N*-oxides exhibited chemical shifts which are interpreted in terms of electronic and compressional effects. The ^{17}O chemical shift for 8-methylquinoline *N*-oxide (370 ppm) is deshielded by 25 ppm more than predicted, based upon electronic considerations. The ^{17}O chemical shift for the *N*-oxide of 8-hydroxyquinoline (289 ppm) is substantially shielded as a result of intramolecular hydrogen bonding. The relative ^{17}O chemical shifts for diazine *N*-oxides of pyrazine, pyridazine and pyrimidine follow predictions based on back donation considerations. Because of solubility limitations, spectra of only two *N,N'*-dioxides were obtained. The chemical shift of benzopyrazine di *N*-oxide in acetonitrile was shielded by 18 ppm compared to that of its mono *N*-oxide.

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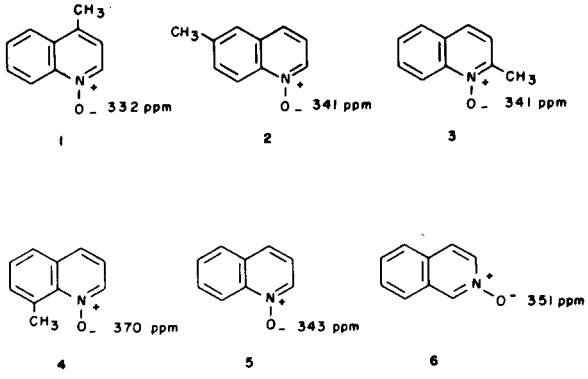
Previous ^{17}O nmr studies on *N*-oxides have focused primarily on pyridine *N*-oxides [1,2]. Investigation of the ^{17}O nmr properties of 4-substituted pyridine *N*-oxides demonstrated that the *N*-oxide ^{17}O chemical shift is extremely sensitive to electronic and solvent effects [1]. In addition, steric effects have been shown to play a significant role in determining the ^{17}O chemical shifts of 2-substituted pyridine *N*-oxides [2]. Because of the unique chemical and physical properties of the *N*-oxide functional group [3-6], determination of the ^{17}O nmr spectral properties of a number of different heterocyclic *N*-oxides is of interest. ^{17}O nmr results from *N*-oxides can be used to distinguish between structural isomers [2] and to assess the influence of structural changes upon the electronic distribution of the *N*-oxide group [1]. In this paper we report the ^{17}O chemical shift data for azine *N*-oxides, diazine *N*-oxides and di-*N*-oxides.

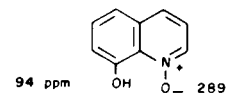
Azine *N*-Oxides.

Earlier studies [2] in this laboratory showed, for a number of 2-substituted pyridine *N*-oxides and for three benzopyridine *N*-oxides, that compressional effects play a significant role in determining ^{17}O chemical shifts. Because of the limited number of benzopyridine *N*-oxides studied, it is important to look at other examples to determine the effect of benzene ring fusion and to compare compressional effects of substituents for the quinoline *N*-oxides, particularly at the 8-position where *peri* interactions are involved, with those of the 2-substituted pyridine *N*-oxides. To this end several isomeric methyl quinoline *N*-oxides, **1-4**, were examined; also values for quinoline *N*-oxide, **5** [2] and isoquinoline *N*-oxide, **6**, are given for reference. Figure 1 contains representative natural abundance ^{17}O spectra for three quinoline *N*-oxides. It is noted



that the chemical shifts for **1** and **3** are shielded by 4-6 ppm compared with those of the appropriate pyridine *N*-oxides [1,2]. This shielding effect has been observed previously for the *N*-oxides of quinoline and two benzoquinolines and appears to be a general effect of benzene ring fusion. The chemical shift of **3** is deshielded by 9 ppm compared to its 4-isomer **1**, which is similar to the chemical shift difference observed for the 2- and 4-methylpyridine *N*-oxides [2]. The electronic effect of the methyl at position-6 is greatly reduced in magnitude compared to that at position-4. Thus, electronic effects of alkyl groups in the heterocyclic ring are comparable to those noted for pyridines [1]; however, the effects of such substituents in the fused benzene ring appear to be more complex. Interestingly, the 8-substituted compound **4** is deshielded by 29 ppm compared to its electronically equivalent isomer **2**. This chemical shift difference represents a compressional effect for the 8-methyl group equivalent to that observed for a 2-*t*-butyl group in the pyridine system [2].

To examine the effect of intramolecular hydrogen-bonding for the *N*-oxide function, 8-hydroxyquinoline *N*-oxide, **7**, was studied. The *N*-oxide signal for **7** at 289 ppm



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(Figure 1) is substantially shielded from that of quinoline *N*-oxide **5**, at 343 ppm. Shielding, attributed to intramolecular hydrogen-bonding, has been noted for the carbonyl oxygens of 5,8-dihydroxynaphthoquinone [7]. The magnitude of the shift for **7**, exclusively attributable to hydrogen-bonding, is difficult to assess. Compressional effects and electronic effects [8] of the 8-hydroxy group upon the *N*-oxide oxygen would be deshielding; consequently, the difference of 54 ppm for the chemical shifts of **5** and **7** can be regarded as the minimum effect due to hydrogen-bonding. It is noted that the hydroxy oxygen (94 ppm) participating in the hydrogen bond is deshielded relative to the signal for phenol (79 ppm) [9] and related phenolic compounds (87 ppm) [7]. Here the determination of the effects arising solely from hydrogen-bonding is even more problematic since the magnitude of compressional effects on single bonded oxygen atoms is not well documented, although they appear to be small [2]. It seems probable that the oxygen of the donor for intramolecular hydrogen-bonding experiences deshielding.

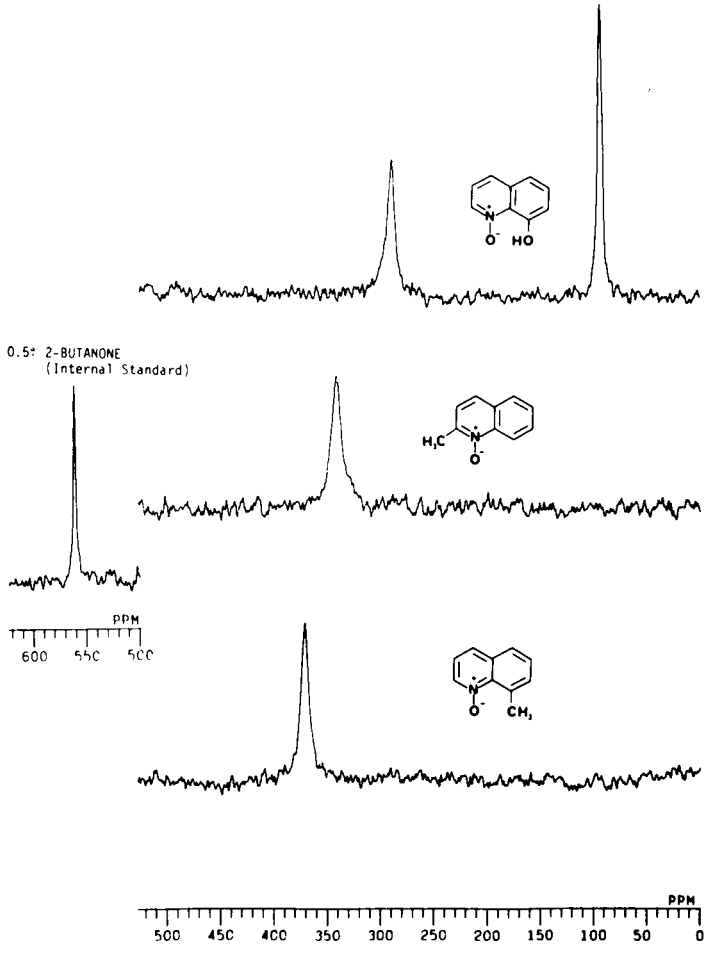
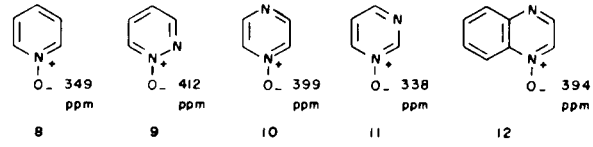


Figure 1. Natural abundance ^{17}O nmr spectra of 8-hydroxyquinoline *N*-oxide, **7**, 2-methylquinoline *N*-oxide, **3**, and 8-methylquinoline *N*-oxide, **4**, in acetonitrile at 75° [insert shows 2-butanone (0.5%) as internal standard].

For quinoline *N*-oxides we have found that compressional effects are similar in magnitude to those noted for pyridine *N*-oxides with the exception of 8-substituted quinolines, where, as a result of the *peri* interaction, the effect is much greater. Substantial intramolecular hydrogen-bonding shifts comparable to those for intermolecular hydrogen-bonding between pyridine *N*-oxide and water are noted [1].

Diazine *N*-Oxides.

The chemical and physical properties of diazine *N*-oxides have been the subject of intense investigation for a number of years [4,5,10,11]. One point of continuing interest has been the relative extent of back donation of electron density from the *N*-oxide oxygen to the ring [10]. Studies of the dipole moments [12], ionization potentials [13], infrared stretching frequencies [14] and ^{1}H, ^{13}C, ^{15}N nmr chemical shifts [10,11] of diazine *N*-oxides have been carried out which examine the relative back donation of various diazine *N*-oxides. Since ^{17}O nmr spectroscopy directly measures properties of the atom in question, it seems ideally suited for studying back donation of such *N*-oxides. The ^{17}O nmr chemical shift values of pyridine *N*-oxide, **8**, [1], of the isomeric diazine *N*-oxides, **9-11**, and of benzopyrazine *N*-oxide, **12**, are shown below. The order

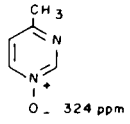


8 9 10 11 12

of ^{17}O chemical shifts is **9** > **10** > **8** > **11**, with the larger value corresponding to the greater double bond character for the NO bond. This order of double bond character is in reasonable agreement with that suggested by Paudler and Jovanovic [10] based upon ^{15}N chemical shifts. The only difference in the bond order estimates based on ^{15}N data and the ^{17}O results is that the former predicts that **8** and **11** should exhibit comparable NO bond orders. The ^{17}O results indicate that back donation is somewhat greater for pyridine *N*-oxide **8** than for pyrimidine *N*-oxide **11**. It is noted that the chemical shift of **9** is downfield from that of **10** by 13 ppm. However, this downfield shift difference may not be solely attributable to differences in back dona-

tion of the two isomers. It is possible that compressional effects of the lone pair of electrons on the adjacent nitrogen are contributing to the deshielding observed for **9**. The ^{17}O chemical shift of the benzodiazine **12** is shielded by 5 ppm compared to its diazine parent **10**. This represents another example of the shielding effect of a benzene ring fusion *ortho* to the *N*-oxide function.

In order to assess the effect of compressional factors on the ^{17}O chemical shifts in the diazine series, we obtained natural abundance spectra for 4-methylpyrimidine 1-oxide, **13**, and 4-methylpyrimidine 3-oxide, **14**. Since the



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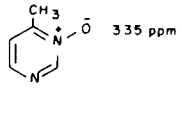

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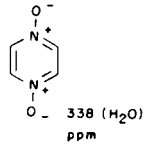
electronic effects of the methyl group in the two isomers **13** and **14** are equivalent, any difference in chemical shift of the two can be attributed to compressional effects. Based upon pyridine *N*-oxide data [1,2], the methyl groups' electronic effect should be shielding for the signal of **13** and **14** by 13 ppm. The 1-oxide, **13**, which should be devoid of compressional effects, exhibits a chemical shift of 324 ppm shielded by 14 ppm compared to **11** in agreement with predictions based upon the pyridine system [2]. The chemical shift of **14** should experience the same degree of shielding (13 ppm) arising from electronic effects as for **13**, but its signal should also be deshielded by 14 ppm arising from compressional effects (based upon pyridine results [2]), resulting in essentially no chemical shift difference with its parent **11**. The chemical shift observed for **14** is 335 ppm in good agreement with the above prediction.

Diazine *N*-Dioxides.

The influence of changing the electron density of the azine *N*-oxides by converting the second nitrogen of diazine to an *N*-oxide group has not been investigated by ^{17}O nmr. To examine this effect, the ^{17}O nmr spectra of pyrazine *N,N'*-dioxide **15** and benzopyrazine *N,N'*-dioxide **16** in ^{16}O normalized water solution were taken. Solubility limitations were found to represent a major problem in ^{17}O



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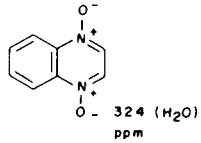

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nmr spectroscopy of di *N*-oxides. For example, phenazine *N,N'*-dioxide is insufficiently soluble in all solvents examined to obtain a natural abundance ^{17}O spectrum. Similarly, a spectrum of **15** could not be obtained in acetonitrile, whereas a spectrum of **16** was obtained in both acetonitrile (376 ppm) and in water. Since it has been previously shown [1] that *N*-oxide shifts undergo enormous shifts in water solution, it is not prudent to make comparisons between the chemical shifts of **15** and **10** in different solvents. However, it was possible to record the spectrum of **10** in water; the value obtained was 334 ppm--65 ppm different from that found in acetonitrile. The difference in the chemical shifts between **10** and **15** in water solution is 4 ppm. Because of the contributions of variable hydrogen-bonding, this result is not interpretable in terms of structural differences. A large water induced shielding effect was also noted for pyridine *N*-oxide [1]. The mono and di *N*-oxides **12** and **16** are the only structurally related pair which were soluble in, the presumably-inert, aprotic solvent, acetonitrile. In this case the dioxide is shielded (18 ppm) compared to its monooxide. Shielding is expected based on the larger degree of single bond character of a di-*N*-oxide compared to that of its mono di-oxide.

EXPERIMENTAL

The *N*-oxides **1** [16], **2** [17], **3** [18], **4** [17], **9-11** [19], **12** [20], **13-14** [21], and **16** [20] were prepared by hydrogen peroxide/acetic acid oxidations. Several, **5-8** and **15** were commercially available (Aldrich and Lancaster Synthesis). The physical data of the compounds were in accord with literature values. The ^{17}O spectra were recorded on a JEOL GX-270 Spectrometer equipped with a 10 mm broad band probe operated at 36.5 MHz. The nmr spectra were acquired at natural abundance on 0.5 *M* solutions for all compounds in dried acetonitrile (distilled over CaH_2 and stored over molecular sieves) at 75°; those obtained in ^{16}O normalized (^{17}O depleted) water (Merck) were on 0.5 *M* solutions at 75°. The chemical shift data were referenced to external water (0.5% 2-butanone was added as an internal check, 558 ±1 ppm). The instrument settings were: 25 KHz spectral width, 2 K data points, 90° pulse angle (28 μs pulse width, determined by a single pulse on a sample of deionized water), 0.3 ms acquisition delay, and 40 ms acquisition time. The spectra were recorded with sample spinning and without lock. The signal-to-noise ratio was improved by applying a 25 - 50 Hz exponential broadening factor to the FID prior to Fourier transformation. The data point resolution was improved to ±0.2 ppm by zero filling to 8 K data points. Spectra with S/N of about 7/1 were obtained after ~10^6 scans. Under these conditions, in acetonitrile, the half height band widths for the single-ring compounds were 250 ±25 Hz, and for the two-ring systems were 350 ±50 Hz; the accuracy of the chemical shifts is estimated to be ±2 ppm.

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