Effects of Electronic Resonance Interaction on the Methoxy Group NMR Parameters. Theoretical and Experimental Study of Substituted 2-Methoxypyridines

Rubén H. Contreras, Rodolfo R. Biekofsky, and Dora G. de Kowalewski

Departmento de Fisica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellon I, Ciudad Universitaria, Buenos Aires (1428), Argentina

Anita M. Orendt† and Julio C. Facelli⊥⊥

Utah Supercomputing Institute and Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

Received: March 30, 1992

In order to increase the understanding of the interactions which define the planar conformation of the methoxy group with respect to the aryl ring in methyl aryl ethers and the effect these interactions have on the methoxy NMR parameters, 17O and 13C spectra were measured and ab initio optimized geometries were calculated for three different conformations of the methoxy group in 2-methoxy-5-X-pyridines (X = H, NO2, and NH2). 17O and 13C chemical shifts were also calculated using the LORG approach. It was found that, contrary to what has been commonly assumed, the oxygen and the carbon of the methoxy group are deshielded when the electronic resonance interaction is increased. Therefore, the large 13C deshielding effect observed for a conformation with an out-of-plane methoxy group in aryl methyl ethers and related compounds has to be attributed to the inhibition of the attractive van der Waals forces between the methyl moiety and the aromatic ortho-cis carbon atom.

Introduction

In a recent paper Bond and Schleyer1 reported the results of an ab initio study indicating that the preferential s-cis conformation in methyl vinyl ether and related compounds originates mainly due to the electrostatic interaction between the methyl and vinyl moieties. The methoxy group in unhindered methyl aryl ethers also adopts a planar conformation2 as in these methyl vinyl ethers, suggesting that electrostatic interactions between the methyl group and the proximate ring atoms may also play an important role in defining the preferential conformation in the methyl aryl ethers. Therefore, it is expected that this electrostatic interaction would complement the resonance interaction between the π-type oxygen lone pair and the aromatic π-electron system in defining the planar conformation.

In this paper, the 17O and 13C NMR shieldings of 2-methoxypyridine (I), 2-methoxy-5-nitropyridine (II), and 2-methoxy-5-aminopyridine (III) are used to estimate the importance of the resonance interaction and the electrostatic interactions in determining the NMR parameters. Compounds II and III were selected because the nitro and amino groups, placed para to the nitrogen atom of pyridine acts like a nitro group attached to a benzene ring. As the nitro and amino groups are of opposite electronic nature (i.e., electron donating versus electron withdrawing), these two compounds are adequate to assess the effect of the resonance interaction on the methoxy 17O and 13C chemical shifts and the methoxy carbon's 1J(CH) coupling constant. In previous studies 17O chemical shieldings have been found to be very sensitive to the π-resonance interaction.3

Ab initio optimized geometries were calculated for three different conformations of the methoxy group in each compound, namely, planar cis to the N atom, A, planar trans to the N atom, B, and perpendicular to the pyridine ring, C (see Scheme I). The LORG method4 was used to calculate the 17O and 13C magnetic shielding constants for the three different conformations for all three compounds. The experimental shielding values are compared with the calculated values to determine the preferred

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1 Department of Chemistry.
2 Utah Supercomputing Institute.
observed. The bond lengths for all three conformations. While an increase in the resonance interaction increases the bond order, the resonance interaction. The bond orders and bond lengths of the I3C chemical shift, both of them are affected in the same manner. A shielding effect of 13 ppm is observed for an out-of-plane conformation of a methoxy group, and it can be assumed that the main interaction between the two nuclei is an inhibition of the resonance. A shielding effect of 13 ppm along with a slight deshielding (1.3 ppm in tetrahydrofuran and 1.89 ppm in dimethyl-β-sulfone) of the methoxy I3C chemical shift is notably more sensitive to the resonance interaction than the OMe I3C deshielding effect yields a deshielding of the methoxy group, is placed para to the methoxy group producing an inhibition of the electronic resonance. A shielding effect of 13 ppm is observed for the I3C chemical shift, and a slight shielding effect, 0.11 ppm, is observed for the methoxy I3C chemical shift. Therefore, it is observed that although the methoxy I3C chemical shift is not as sensitive to the resonance interaction as the 13C chemical shift, both of them are affected in the same sense; i.e., when increasing the resonance interaction, both nuclei are shielded.

It is important to note that this trend does not support the common assumption that the deshielding effect of about 5 ppm observed for an out-of-plane conformation of a methoxy group, with respect to the planar conformation, originates in an inhibition of resonance.10-14 According to values reported in Table I, an inhibition of resonance would yield a shielding chemical shift and not a deshielding value.

According to values reported in Table I, the OMe I(CH) coupling also seems to be a fairly sensitive probe to this resonance interaction, with the coupling increasing as the resonance interaction increasing.

Calculations. The calculated total energies for the three conformations depicted in Scheme I are shown in Table II. According to those values, in all the compounds studied here the preferred conformation is planar-cis, as is expected from the experimental data.1 The trans-cis difference increases slightly when increasing the resonance interaction, going from 30.46 kJ/mol in III to 32.17 kJ/mol in II, indicating that the resonance interaction favors the planar-cis over the planar-trans conformation. While for compound II the planar-trans conformation is preferred over the perpendicular orientation, for I and III the opposite holds.

Other calculated molecular parameters are also affected by the resonance interaction. The bond orders and bond lengths of the Caryl-O and O-CMe bonds are displayed in Table III for all three conformations. While an increase in the resonance interaction increases the bond order Pco, a decrease in POMe is observed. The bond lengths Rco and Romet also show opposite effects with the former being lengthened and the latter being shortened when the resonance interaction is increased.

In Table IV the LORG calculated chemical shifts are compared with the experimental values. It is observed that the LORG method with D95 basis set systematically underestimates the chemical shifts by about 40 ppm but successfully reproduces the substituent effects when the experimental values are compared with those calculated for the A conformations. The 13C chemical shielding constants are underestimated by about 10 ppm, but again the qualitative trends are well reproduced.

The theoretical calculations confirm the experimental trend that resonance interactions affect both nuclei in the same sense; i.e., when the resonance interaction is increased both nuclei are deshielded, and when there is an inhibition of the resonance interaction both nuclei are shielded.

For the B conformations the 13O SCS are essentially the same as those obtained for the A conformations. As 13C chemical shifts are quite sensitive to resonance interactions,5 this indicates that the resonance interaction between the methoxy and nitro or amino groups is essentially the same for both planar conformations.

It is important to observe that for the methoxy out-of-plane conformation, C, the SCS effects are smaller than those observed for the planar forms, but they are still significant. This is a clear indication that even for an out-of-plane conformation the methoxy group is undergoing a rather strong resonance interaction with the electronic system. This result is in agreement with recent experimental results on sterically crowded methoxy groups in substituted anisoles.15 The calculated 13C SCS for the O conformations show the rather strong 13C deshielding effect of about 6 ppm previously observed in other aromatic compounds.11,16

Conclusions
Both experimental and theoretically calculated 17O and 13C chemical shifts indicate that in compounds I--III the increase in

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**Table I**: 13C and 17O Chemical Shifts and I(CH) Couplings of the Methoxy Moiety in 2-Methoxy-5-X-pyridines

| compd | X | 13C | 17O | I(CH) |
|-------|---|-----|-----|------|
| I     | H | 53.10 (52.80)* | 70 | 145.3 |
| II    | NO2| 54.40 (54.69)* | 86 | 147.4 |
| III   | NH3| 52.99 | 57 | 144.6 |

* Chemical shifts in ppm, I(CH) in Hz. 17O values are externally referenced to water at 28 °C and were measured in pyridine-d5. 13C values referenced to TMS at room temperature and were measured in tetrahydrofuran. In dimethyl-β-sulfone, taken from: Barlin, G. B.; Fenn, M. D. Heterocycles 1986, 24, 1301.

**Table II**: Calculated Total Energies for Compounds I--III as a Function of Conformation

| conformation | compound |
|--------------|----------|
| I            | II       | III      |
| A            | 360.479 441 | -563.878 467 | -415.493 954 |
| B            | 360.467 444 | -563.866 044 | -415.482 294 |
| C            | 360.467 693 | -563.864 437 | -415.484 725 |

* All values are in au. * Conformations are shown in Scheme I.

**Table III**: Bond Orders, P, and Bond Lengths, R, of the Caryl-O and O-CMe Bonds in Different Conformations of 2-Methoxy-5-X-pyridines

| compd | Pco | POMet | Rco | Romet |
|-------|-----|-------|-----|-------|
| IA    | 0.2132 | 0.1649 | 1.357 | 1.445 |
| IB    | 0.2134 | 0.1670 | 1.363 | 1.436 |
| IC    | 0.1603 | 0.1830 | 1.374 | 1.446 |
| IIA   | 0.2354 | 0.1527 | 1.342 | 1.451 |
| IIB   | 0.2233 | 0.1583 | 1.347 | 1.442 |
| IIC   | 0.1663 | 0.1742 | 1.362 | 1.453 |
| IIIA  | 0.2054 | 0.1700 | 1.357 | 1.441 |
| IIIB  | 0.1974 | 0.1740 | 1.373 | 1.433 |
| IIIC  | 0.1602 | 0.1888 | 1.388 | 1.443 |

* Bond orders in au, bond lengths in Å. * Conformations are defined in Scheme I. * CO is the Caryl-O bond and OMe is the O--CMe bond.

**Table IV**: LORG Calculated 17O and 13C Chemical Shielding Constants of the Methoxy Group for Compounds I--III as a Function of Conformation

| compd | q(17O) | SCS(17O) | q(13C) | SCS(13C) |
|-------|--------|---------|--------|---------|
| IA    | 195.2 (237.9) | 142.2 (132.3) |
| IB    | 181.3 | 143.1 |
| IC    | 211.7 | 135.9 |
| IIA   | 175.3 (221.9) | -19.9 (-16.0) | 139.5 (131.0) | -2.7 (-1.3) |
| IIB   | 161.4 | -19.9 | 140.6 | -2.5 |
| IIC   | 199.6 | -12.1 | 133.7 | -2.2 |
| IIIA  | 208.1 (250.9) | +12.9 (13.0) | 143.4 (132.4) | +1.2 (0.1) |
| IIIB  | 193.5 | +12.2 | 143.5 | +0.4 |
| IIIC  | 218.4 | +6.7 | 136.9 | +1.0 |

* All values are in ppm. 13O and 13C magnetic shielding constants are referenced to the bare nucleus. SCS are taken as the difference between the calculated value and that of I in the same conformation. Experimental values are given in parentheses. The experimental chemical shifts from Table I were converted to absolute shieldings using δOMe = 307.9 ppm and δTMS = 185.4 ppm. * Conformations are shown in Scheme I.
the resonance interaction produces a deshielding effect on both the carbon and oxygen of nuclei of the methoxy group. Moreover, according to the calculations this holds for both an in-plane and an out-of-plane methoxy group conformation. As a similar behavior can be expected in other methyl aryl ethers, the well-known deshielding effect of the methoxy $^{13}$C chemical shift for an out-of-plane conformation cannot originate in an inhibition of resonance as it has been commonly assumed.$^{10-13}$

In substituted anisoles the conformational effect of the methoxy group on the chemical shift of the aromatic ortho carbon atom placed cis to the methyl moiety is a shielding effect of approximately 8 ppm;$^{16,17}$ therefore, it can be concluded that the proximity between the methyl moiety and the aromatic ring yields a shielding effect on both $^{13}$C nuclei. According to Li and Chestnut,$^{18,19}$ when two atoms of the same molecule are in close proximity to one another, a shielding effect is observed on both if the van der Waals forces yield an attractive interaction, while a deshielding effect is observed if there is a repulsive interaction. These considerations suggest that the observed shielding effect is due to an attractive interaction.

These attractive interactions are similar in nature to those described as electrostatic interactions by Bond and Schleyer$^1$ when they analyzed the interactions that define the preferential $s$-cis conformation in vinyl methyl ether and related compounds. Therefore, it can be concluded that in methyl aryl ethers two different types of interactions cooperate to define a planar methoxy conformation, namely, the conjugative interaction between the oxygen $\pi$-type lone pair and the aromatic $\pi$ electronic system and the electrostatic attraction between the methyl moiety and the aromatic ortho-cis carbon atom.

**Acknowledgment.** The XL-400 spectrometer was funded by the NSF (Grant 83-14771). Grants from the NSF (INT 86-12463), CONICET (Argentina), and UBA (Argentina) are gratefully acknowledged. Computational time was provided by the Utah Supercomputing Institute, which is funded by the State of Utah and the IBM Corp.