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

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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, ^{17}O and ^{13}C 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, NO$_2$, and NH$_2$). ^{17}O and ^{13}C 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 ^{13}C 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 Schleyer[1] 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 conformation[2] 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 ^{17}O and ^{13}C 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 methoxy group, can interact with the methoxy group only by electronic resonance through the π-system. 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 ^{17}O and ^{13}C chemical shifts and the methoxy carbon's ^1J(CH) coupling constant. In previous studies ^{17}O 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 method[4] was used to calculate the ^{17}O and ^{13}C 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

SCHEME I

X = H, NO$_2$, NH$_2$
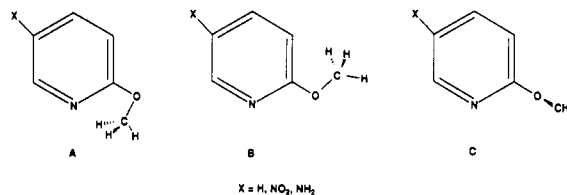
conformation. In all three cases A is expected to be the preferred conformation.[5]

Experimental Section

NMR Measurements. Natural abundance ^{13}C NMR spectra were recorded on a Varian FT-80A spectrometer using D$_2$O as an external lock. The spectra were recorded at room temperature in tetrahydrofuran. ^{13}C chemical shifts were referenced internally to TMS.

Natural abundance ^{17}O NMR spectra were recorded on a Varian XL-400 spectrometer using 5-mm sample tubes. Spectra were taken at room temperature in pyridine-d_5. ^{17}O chemical shifts were externally referenced to water at 28 °C.

All substances were of commercial origin.

Calculations. Geometry optimizations were carried out for compounds I–III, for the three different conformations A–C, using the GAUSSIAN-86 molecular package.[6] In the optimization of the A and B structures the C_s symmetry was enforced. The D95 basis set was employed.[7] Methoxy ^{17}O and ^{13}C magnetic shielding constants were calculated for all optimized geometries using the LORG program[4] with the same basis set.

Results and Discussion

NMR Measurements. The methoxy ^{17}O and ^{13}C chemical shifts and ^1J(CH) coupling in I–III are shown in Table I. A large ^{17}O deshielding is observed in I relative to the shielding measured in anisole (45 ppm).[8] This deshielding effect can be attributed to the resonance interaction between two substituents placed ortho to one another, assuming that electronically the ring nitrogen atom of pyridine acts like a nitro group attached to a benzene ring.[9]

TABLE I: ^{13}C and ^{17}O Chemical Shifts and ^1J(CH) Couplings of the Methoxy Moiety in 2-Methoxy-5-X-pyridines[a]

compd	X	^{13}C	^{17}O	^1J(CH)
I	H	53.10 (52.80[b])	70	145.3
II	NO$_2$	54.40 (54.69[b])	86	147.4
III	NH$_2$	52.99	57	144.6

[a] Chemical shifts in ppm, ^1J(CH) in Hz. ^{17}O values are externally referenced to water at 28 °C and were measured in pyridine-d_5. ^{13}C values referenced to TMS at room temperature and were measured in tetrahydrofuran. [b] In dimethyl-d_6 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[a]

	compound		
conformation[b]	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

[a] All values are in au. [b] Conformations are shown in Scheme I.

Compound II contains an electron acceptor, the nitro group, placed para to the methoxy group, which is an electron donor, and it can be assumed that the main interaction between the two groups is a resonance interaction. The increase of the resonance effect yields a deshielding of the methoxy ^{17}O chemical shift of 16 ppm along with a slight deshielding (1.3 ppm in tetrahydrofuran and 1.89 ppm in dimethyl-d_6 sulfone) of the methoxy ^{13}C chemical shift. In compound III an electron donor substituent, the amino 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 ^{17}O chemical shift, and a slight shielding effect, 0.11 ppm, is observed for the methoxy ^{13}C chemical shift. Therefore, it is observed that although the methoxy ^{17}O chemical shift is notably more sensitive to the resonance interaction than the ^{13}C 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 ^1J(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.[5] 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 C$_{aryl}$–O and O–C$_{Me}$ bonds are displayed in Table III for all three conformations. While an increase in the resonance interaction increases the bond order P_{CO}, a decrease in P_{OMe} is observed. The bond lengths R_{CO} and R_{OMe} also show opposite

TABLE III: Bond Orders, P, and Bond Lengths, R, of the C$_{aryl}$–O and O–C$_{Me}$ Bonds in Different Conformations of 2-Methoxy-5-X-pyridines[a]

compd[b]	P_{CO}[c]	P_{OMe}[c]	R_{CO}[c]	R_{OMe}[c]
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	1.367	1.441
IIIB	0.1974	0.1740	1.373	1.433
IIIC	0.1602	0.1888	1.388	1.443

[a] Bond orders in au, bond lengths in Å. [b] Conformations are defined in Scheme I. [c] CO is the C$_{aryl}$–O bond and OMe is the O–C$_{Me}$ bond.

TABLE IV: LORG Calculated ^{17}O and ^{13}C Chemical Shielding Constants of the Methoxy Group for Compounds I-III as a Function of Conformation[a]

compd[b]	σ(^{17}O)	SCS(^{17}O)	σ(^{13}C)	SCS(^{13}C)
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

[a] All values are in ppm. ^{17}O and ^{13}C 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 δ_{H_2O} = 307.9 ppm and δ_{TMS} = 185.4 ppm.[14] [b] Conformations are shown in Scheme I.

effects with the former being lengthened and the latter being shortened when the resonance interaction is increased.

In Table IV the LORG calculated chemical shieldings are compared with the experimental values. It is observed that the LORG method with D95 basis set systematically underestimates the chemical shieldings by about 40 ppm but successfully reproduces the substituent effects when the experimental values are compared with those calculated for the A conformations. The ^{13}C chemical shieldings are overestimated 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 ^{17}O SCS are essentially the same as those obtained for the A conformations. As ^{17}O chemical shifts are quite sensitive to resonance interactions,[3] 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 π electronic system. This result is in agreement with recent experimental results on sterically crowded methoxy groups in substituted anisoles.[15] The calculated ^{13}C shieldings for the C conformations show the rather strong ^{13}C deshielding effect of about 6 ppm previously observed in other aromatic compounds.[11,16]

Conclusions

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

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 π-type lone pair and the aromatic π electronic system and the electrostatic attraction between the methyl moiety and the aromatic ortho-cis carbon atom.

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