

Ab Initio and ^{17}O NMR Study of Aromatic Compounds with Dicoordinate Oxygen Atoms.

2. Intramolecular Hydrogen Bonding in Hydroxy- and Methoxybenzene Derivatives^{†,1}

Anita M. Orendt,

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

Rodolfo R. Biekofsky,[‡] Alicia B. Pomilio,[§]

Departamento de Química Organica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellon II, Ciudad Universitaria, Buenos Aires (1428), Argentina

Ruben H. Contreras,[§]

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

and Julio C. Facelli*

Utah Supercomputing Institute and Department of Chemistry, University of Utah, Salt Lake City, Utah 84112
(Received: January 22, 1991)

The ^{17}O chemical shifts of several ortho-substituted phenols and anisoles are presented along with those of the corresponding para-substituted compounds. The measurements of the various ortho-para pairs were done in the same solvent and at the same temperature in order to experimentally estimate the effect of intramolecular hydrogen bonding on the ^{17}O chemical shielding in the ortho compounds by using the ortho-para equivalence rule. Ab initio calculations of the ^{17}O chemical shieldings reproduce well the experimental findings and provide a theoretical description of the hydrogen-bonding effect on the ^{17}O chemical shifts.

Introduction

Hydrogen bonding, HB, is widely recognized as a fundamental feature in chemical and biological systems² and ^{17}O NMR spectroscopy appears to be especially suited to study HB since the oxygen atom is directly involved in the formation of the bond. ^{17}O chemical shifts can provide useful information on the strength of the HB, the OH distance, and other molecular properties.³ The dominance of intramolecular HB effects over substituent effects in the ^{17}O chemical shifts of carbonyl groups has been clearly demonstrated for a variety of compounds.³⁻⁵ However, the effect of proton donation on ^{17}O chemical shift of the hydroxy group was determined to be considerably smaller than that on the carbonyl oxygen chemical shifts. The HB-induced changes in the ^{17}O chemical shifts of the methoxy groups in *o*-anisic acid and *o*-anisamide have been measured as shielding effects as for hydrogen bonding of the carbonyl group. However, the shift changes observed are an order of magnitude smaller.⁶ Since intramolecular HB effects are small and comparable in magnitude to electronic and steric substituent effects in compounds with dicoordinate-oxygen-containing functions, it is necessary to determine the relative contributions of each of these competing effects in order to be able to interpret the ^{17}O chemical shifts of these compounds.

Quantum chemical calculations provide a powerful tool for structural analysis because in the calculations it is possible to control structural effects which cannot be varied in actual experiments without also introducing major changes in the electronic effects. Here quantum chemical calculations of the ^{17}O chemical shielding for ab initio optimized structures are used to elucidate the different electronic and structural contributions to the ^{17}O chemical shieldings.

In this paper the ^{17}O chemical shifts are reported for a number of substituted phenols and anisoles in which intramolecular HB

is known to be present. The analysis of the experimental results is based on the assumption of para-ortho equivalence of the electronic effects; thus, the difference in the ^{17}O chemical shieldings of the corresponding ortho- and para-substituted compounds can be assigned to HB interactions, which are present only in the ortho-substituted compounds. A detailed analysis of the quantum mechanical origin of the shifts observed due to the HB interaction is also presented. The theoretical calculations of the ^{17}O chemical shieldings of the studied compounds strongly support the use of the para-ortho equivalence rule for the analysis of the substituent effects on ^{17}O chemical shieldings.

Experimental Section

Materials. All the compounds were obtained commercially or synthesized by using standard methods. No sample showed any impurity by proton and carbon NMR spectroscopy.

NMR Measurements. The natural abundance ^{17}O chemical shifts were recorded on either a Varian XL-400 (compounds 1, 2, and 8) or on a Varian VXR-500 spectrometer. On the XL-400 5-mm samples were used. Pertinent spectral parameters include pulse width of 7 μs (90 of 20 μs), acquisition time 0.25 s, and recycle time of 0.25 s. On the VXR-500, 10-mm samples were used with 6- μs pulse (90 of 20 μs) and 0.05-s acquisition time. All samples except 6 and 7 were measured in toluene-*d*₈ (Aldrich, 99+%D) at 75 °C. Since compound 6 was not soluble in toluene, the spectra of the ortho-para pair 6 and 7 were recorded in

(1) Part 1 of this work: Biekofsky, R. R.; Pomilio, A. B.; Contreras, R. H.; Orendt, A. M.; Facelli, J. C. *J. Phys. Chem.* **1990**, *94*, 7418.

(2) Shuster, P., Zundel, G., Sandorfy, C., Eds. *The Hydrogen Bond: Recent Developments in Theory and Experiments*; North Holland: Amsterdam, 1976; Vol. I, II, and III.

(3) Jaccard, G.; Lauterwien, J. *Helv. Chim. Acta* **1986**, *69*, 1469.

(4) St. Amour, T. E.; Burgar, M. I.; Valentine, B.; Fiat, D. *J. Am. Chem. Soc.* **1981**, *103*, 1128.

(5) Boykin, D. W., Ed. *^{17}O NMR Spectroscopy in Organic Chemistry*; CRC Press: Boca Raton, 1990.

(6) Jaccard, G.; Carrupt, A.; Lauterwien, J. *Magn. Reson. Chem.* **1989**, *26*, 239.

[†] Part of a Ph.D. Thesis (R.R.B.) to be presented to the University of Buenos Aires.

[‡] With a Research Fellowship from the Argentine National Research Council (CONICET).

[§] Research member of the Argentine National Research Council (CONICET).

TABLE I: Natural Abundance Hydroxy ^{17}O Chemical Shifts in Substituted Phenols^a

compound	$\delta(^{17}\text{O})$	compound	$\delta(^{17}\text{O})$
phenol (1)	71	2-hydroxybenzaldehyde (5)	80 ^c
4-methoxyphenol (2)	64	4-nitrophenol (6)	88 ^d
2-methoxyphenol (3)	52	2-nitrophenol (7)	82 ^e
4-hydroxybenzaldehyde (4)	85 ^b		

^a All values reported in ppm referenced to H_2O at room temperature; experimental conditions and solvents are described in the text. ^b Aldehyde ^{17}O shift at 548 ppm. ^c Aldehyde ^{17}O shift at 570 ppm. ^d Nitro ^{17}O shifts at 561 ppm. ^e Nitro ^{17}O shifts at 560 ppm.

TABLE II: Natural Abundance Methoxy ^{17}O Chemical Shifts in Substituted Anisoles^a

compound	$\delta(^{17}\text{O})$	compound	$\delta(^{17}\text{O})$
anisole (8)	45	4-methoxyaniline (9)	33
4-methoxyphenol (2)	37	2-methoxyaniline (10)	29
2-methoxyphenol (3)	25		

^a All values given in ppm referenced to H_2O at room temperature; experimental conditions and solvents are described in the text.

methylene- d_2 chloride (Aldrich, 99+%D) at 28 °C. The concentrations of all the samples studied here were close to saturation. All ^{17}O chemical shifts were externally referenced to H_2O at the sample temperature and then corrected to H_2O at 28 °C being 0.0 ppm. The chemical shift of H_2O at 75 °C was -2.6 ppm.

Calculations. The calculations of the ^{17}O chemical shielding were performed using the LORG program⁷ with the D95 basis set.⁸ All the calculations were done using fully optimized structures obtained with the GAUSSIAN 86 molecular package⁹ and the D95 basis.⁸ The calculated values of shielding are reported as absolute values, i.e., shifts measured with respect to the bare nucleus. For comparison, the experimental data were converted to the absolute scale by using an absolute shielding of 307.9 ppm for H_2O . The local bond analysis was performed as described in detail elsewhere.¹⁰

Results and Discussion

The ^{17}O chemical shifts of the substituted phenols and substituted anisoles are given in Tables I and II, respectively. For all ortho-para pairs studied, the ^{17}O chemical shift of the ortho-substituted compound is upfield from that of the para-substituted compound.

Substituent ^{17}O chemical shifts at the ortho position can be influenced by electronic, proximity, and anisotropy effects.¹¹ However, magnetic anisotropy effects on ^{17}O chemical shifts can be neglected here since they are much smaller than the other contributions, being important only in proton chemical shifts.¹² Ortho-substituent electronic effects can be estimated considering that they are, in general, similar to those of para substituents (ortho-para equivalence). In turn, proximity effects can be separated into steric and hydrogen bond contributions. In order to be able to estimate each of these contributions it is assumed that they are essentially independent. From the experimental data it is clear that when ortho substituents can interact through HB, significant departures from the ortho-para equivalence rule are

(7) Hansen, Aa. E.; Bouman, T. D. *J. Chem. Phys.* **1985**, *82*, 5035.

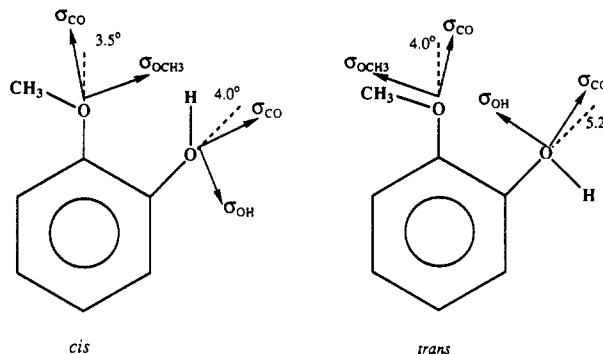
(8) Dunning, T. H.; Hay, P. J. In *Methods in Electronic Structure Theory*; Schaefer III, H. F., Ed.; Plenum Press: New York, 1977.

(9) Frisch, M. J.; Binkley, J. S.; Schlegel, H. B.; Raghavachari, K.; Melius, C. F.; Martin, R. L.; Stewart, J. J. P.; Bobrowicz, F. W.; Rohlfing, C. M.; Kahn, L. R.; Defrees, D. J.; Seeger, R.; Whiteside, R. A.; Fox, D. J.; Fleuder, E. M.; Pople, J. A. Carnegie-Mellon Quantum Chemistry Publishing Unit, Pittsburgh, PA, 1984.

(10) (a) Facelli, J. C.; Grant, D. M.; Michl, J. *Int. J. Quantum Chem.* **1987**, *31*, 45. (b) Solum, M. S.; Facelli, J. C.; Michl, J.; Grant, D. M. *J. Am. Chem. Soc.* **1986**, *108*, 6464. (c) Facelli, J. C.; Grant, D. M. *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H. Eds.; Wiley: New York, 1989; Vol. 19, p 1.

(11) (a) Boykin, D. W.; Hertzler, R. L.; Delphon, J. K.; Eigenbraun, E. *J. J. Org. Chem.* **1989**, *54*, 1418. (b) Boykin, D. W.; Bumstart, A. L. *Tetrahedron* **1989**, *45*, 3613.

(12) Ditchfield, R.; Ellis, P. D. In *Topics in Carbon-13 NMR Spectroscopy*; Levy, G. C., Ed.; Wiley: New York, 1974; Vol. 1, p 1.

**Figure 1.** Orientation of the calculated ^{17}O chemical shielding principal axes for the cis and trans conformations of 2-methoxyphenol.**TABLE III: ^{17}O Calculated LORG Chemical Shieldings^a**

	OH	OCH ₃
phenol (1)	197 (237)	
anisole (8)		212 (263)
4-methoxyphenol ^b (2)	203 (244)	216 (271)
2-methoxyphenol (3)		
cis ^c	212 (256)	240 (283)
trans ^c	200	215

^a All values in ppm, absolute shieldings, i.e., larger values indicate shielding or upfield shift. Experimental values given in parentheses were converted to the absolute shielding scale using $\sigma_{\text{H}_2\text{O}} = 307.9$ ppm.¹⁵ ^b The relative conformation of the side chains does not affect the calculated ^{17}O chemical shieldings. ^c Indicates the relative orientation of the side chains; cis corresponds to the situation in which there is HB between the hydrogen in the hydroxy group and the oxygen in the methoxy group (see Figure 1).

TABLE IV: Calculated ^{17}O Chemical Shielding Tensors in 2-Methoxyphenol^a

	OH			OCH ₃		
	$\sigma_{\text{C-O}}$	$\sigma_{\text{O-H}}$	σ_{\perp}	$\sigma_{\text{C-O}}$	$\sigma_{\text{O-H}}$	σ_{\perp}
cis	234.7	147.1	255.4	274.4	157.1	287.7
trans	251.5	139.6	207.5	248.6	125.7	270.7

^a All values in ppm in absolute shieldings. $\sigma_{\text{C-O}}$ and $\sigma_{\text{O-H}}$ are in the plane of the benzene ring with the actual orientations as depicted in Figure 1. σ_{\perp} is perpendicular to the plane of the benzene ring.

observed, indicating large contributions from the steric and/or HB interactions.

The hydroxy conformation in 2-methoxyphenol has been shown to be cis (see Figure 1) resulting in an intramolecular hydrogen bond of apparently intermediate strength.¹³ This conformation is also predicted to be the most stable one by our ab initio calculations, being 7.9 kcal/mol more stable than the trans conformation. Experimentally, the hydroxy ^{17}O resonance of 2-methoxyphenol is shielded 19 ppm with respect to that of phenol whereas in 4-methoxyphenol it is shielded only by 7 ppm. Assuming then the ortho electronic effect of the methoxy group to be -7 ppm leads to a proximity effect of -12 ppm. By considering any other effect to be negligible, this 12 ppm upfield shift can be attributed to the proton donor effect in the HB.

Similar reasoning can be applied to the other pairs of compounds in Table I, leading to ortho proximity effects of -5 and -6 ppm for the formyl- and nitro-substituted phenols, respectively. Therefore, the effect of proton donation on the hydroxy ^{17}O chemical shift can be estimated to be an upfield shift of 5-12 ppm.

The data in Table II can likewise be interpreted as the result of upfield shifts of 12 and 4 ppm, respectively, for the ortho-substituted of the 2/3 and 9/10 pairs as a consequence of accepting the proton in HB formation.

Calculations of the ^{17}O chemical shielding of phenol, anisole, 4-methoxyphenol, and 2-methoxyphenol (both cis and trans conformations) are presented in Table III. The calculated values

(13) Schaefer, T.; Wildman, T. A. *Can. J. Chem.* **1979**, *57*, 450.

TABLE V: LORG Paramagnetic Bond Contributions to the ^{17}O Chemical Shielding of the Hydroxy Oxygen in 2-Methoxyphenol^a

bond	cis			trans		
	\hat{i}	\hat{j}	\hat{k}	\hat{i}	\hat{j}	\hat{k}
$\text{C}_{\text{Ar}}\text{-O}$	-0.1	4.2	0	-0.8	5.9	0
	4.2	-46.2	0	5.9	-42.8	0
	0	0	-37.8	0	0	-59.5
O-H	-0.2	2.1	0	-0.2	-1.9	0
	2.1	-19.8	0	-1.9	-15.7	0
	0	0	-49.6	0	0	-51.5
O_{ip}^b	-0.1	6.4	± 6.4	-0.5	-9.0	± 2.1
	6.4	-78.6	∓ 10.0	-9.0	-71.3	∓ 0.8
	± 6.4	∓ 10.0	-151.7	± 2.1	∓ 0.8	-166.9

^aAll values in ppm. The bond contributions are expressed in the local bond frame described elsewhere.¹⁰ The orientation of the local bond axis is \hat{i} along the bond; \hat{j} perpendicular to the bond and in the plane of the bond and the $\text{C}_{\text{Ar}}\text{-O}$ bond; \hat{k} perpendicular to \hat{i} and \hat{j} . For the $\text{C}_{\text{Ar}}\text{-O}$ bond the \hat{j} component lies perpendicular to the bond in the plane of the benzene ring. ^bThe \pm signs correspond to the two different lone pairs above and below the molecular plane of the benzene ring, respectively.

compare well with the experimental ones with a correlation coefficient between experimental and calculated values of 0.94; the slope of the correlation is 1.09 and the intercept 26.0 ppm. The ^{17}O shieldings for the cis conformation were used for the 2-methoxyphenol in the correlation. Without including an analysis of solvent effects, very important in ^{17}O chemical shieldings^{5,14} but not included in the calculations, it is not possible to speculate on the origins of the deviations between the calculated and experimental data.

It is remarkable how well the calculations reproduce the ortho-para equivalence in the trans conformation of 2-methoxyphenol in which the HB interactions are not present, while significant departures from this rule, 9 ppm for the hydroxy oxygen and 24 ppm for the methoxy oxygen, are observed in the cis conformation. For both OH and OCH_3 , the HB interaction shifts the ^{17}O resonances upfield as observed experimentally. The calculated shift change of 9 ppm for the hydroxy group on hydrogen bonding agrees very well with the experimental shift difference of 12 ppm whereas the calculated shift difference of 24 ppm for the methoxy oxygen overestimates the experimental value of 12 ppm by a factor of 2.

The calculated ^{17}O shielding tensors for the hydroxy and methoxy oxygens of the cis and trans configurations of compound 2 are presented in Table IV while the orientations of the two in-plane principal components are shown in Figure 1. For the hydroxy oxygen the two principal components in the benzene plane shift in opposite directions: the component which lies approximately along the C-O bond moves downfield and the component nearly perpendicular to this bond moves slightly upfield. The component perpendicular to the benzene ring shows a much larger upfield shift and accounts for most of the upfield shift observed in the isotropic chemical shift. All the principal components move upfield by significant amounts for the methoxy oxygen. Unfortunately, there are no experimental data available on the ^{17}O chemical shielding tensors to compare with these calculated values.

To obtain a better understanding of the origin of these upfield shifts, a detailed analysis of the LORG local bond contributions¹⁰ to the ^{17}O chemical shieldings was conducted. The LORG local bond contributions are presented in Tables V and VI for the hydroxy and methoxy oxygen shielding tensors, respectively. It is apparent from Table V that the bond contribution to the hydroxy oxygen shielding from the OH bond is almost independent of the conformation; i.e., this contribution is not affected by hydrogen bonding. The other two bond contributions are much more sensitive to the hydrogen bonding, with $\sigma_{\hat{k}\hat{k}}^{\text{C}_{\text{Ar}}\text{-O}}$ reduced (less

TABLE VI: LORG Paramagnetic Bond Contributions to the ^{17}O Chemical Shielding of the Methoxy Oxygen in 2-Methoxyphenol^a

bond	cis			trans		
	\hat{i}	\hat{j}	\hat{k}	\hat{i}	\hat{j}	\hat{k}
$\text{C}_{\text{Ar}}\text{-O}$	-0.7	-5.5	0	-1.6	-9.1	0
	-5.5	-43.1	0	-9.1	-55.2	0
	0	0	-32.6	0	0	-38.2
O-CH_3	-1.3	5.0	0	-1.7	6.5	0
	5.0	-7.8	0	6.5	-16.1	0
	0	0	-33.8	0	0	-37.4
O_{ip}^b	-0.7	8.1	± 13.9	-0.4	11.5	± 9.1
	8.1	-74.0	∓ 11.4	11.5	-82.2	∓ 10.6
	± 13.9	∓ 11.4	-144.4	± 9.1	± 10.6	-158.3

^aAll values in ppm. The bond contributions are expressed in the local bond frame described elsewhere.¹⁰ The orientation of the local bond axis is \hat{i} along the bond; \hat{j} perpendicular to the bond and in the plane of the bond and the $\text{C}_{\text{Ar}}\text{-O}$ bond; \hat{k} perpendicular to \hat{i} and \hat{j} . For the $\text{C}_{\text{Ar}}\text{-O}$ bond the \hat{j} component lies perpendicular to the bond in the plane of the benzene ring. ^bThe \pm signs correspond to the two different lone pairs above and below the molecular plane of the benzene ring, respectively.

paramagnetic) by 21.7 ppm and $\sigma_{\hat{k}\hat{k}}^{\text{O}}^b$ by 15.2 ppm in the cis compared to the trans conformation. These large reductions in the paramagnetic contribution are mainly responsible for the OH resonance being much more upfield in the cis conformation.

In the local bond frame it is easy to understand the origin of these conformational effects.¹⁰ Hydrogen bonding of the hydroxy group stabilizes the O-H bond and thereby increases the energy of the O-H antibonding orbital. This antibonding orbital mixes, through the angular momentum operator, with the $\text{C}_{\text{Ar}}\text{-O}$ and O_{ip} occupied orbitals. Therefore, the shielding contributions of these bonds along the direction perpendicular to the benzene plane are significantly reduced by the stabilization of the O-H bond which can occur only in the cis conformation.

All bond contributions to the methoxy ^{17}O shielding show significant upfield shifts in the cis configuration because all the occupied orbitals directly attached to the methoxy oxygen can be coupled, through the angular momentum operator, with at least one of the antibonding methoxy oxygen lone pairs. Therefore, lowering the energy of the oxygen lone pairs by hydrogen bonding reduces the paramagnetic bond contributions of all these bonds in the directions perpendicular to the bonds.

Conclusions

The experimental results presented here demonstrate that significant departures of ^{17}O chemical shieldings from well-established substituent effect rules, such as ortho-para equivalence can, in certain cases, be attributed to HB effects.

Ab initio calculations of ^{17}O chemical shieldings using the LORG method and moderate basis sets reproduce the experimental findings well. The theoretical calculation along with the analysis of the LORG bond contributions provides a detail analysis of the upfield shifts observed for 2-methoxyphenol due to hydrogen bonding. The upfield shifts of both OH and OCH_3 can be traced back to the stabilization of the molecular orbitals engaged in the hydrogen bond. Thus the analysis of the full ^{17}O chemical shielding tensors may provide detailed information on HB interactions.

Acknowledgment. J.C.F. and A.M.O. thank Professor David M. Grant for his hospitality. The Varian XL-400 spectrometer was funded by NSF (CHE 83-14771). Grants from the Argentine National Research Council (CONICET), University of Buenos Aires, the National Science Foundation (INT 86-12463), and the National Institutes of Health (GM 08521-30) and computer time from the Utah Supercomputing Institute, which is funded by the State of Utah and the IBM Corporation, are gratefully acknowledged.

Registry No. 1, 108-95-2; 2, 150-76-5; 3, 90-05-1; 4, 123-08-0; 5, 90-02-8; 6, 100-02-7; 7, 88-75-5; 8, 100-66-3; 9, 104-94-9; 10, 536-90-3.

(14) Kintzinger, J. P. *NMR Princ. Prog.* 1981, 17, 1.

(15) Jamenson, C. G.; Mason, J. In *Multinuclear NMR*; Mason, J., Ed.; Plenum: New York, 1987.