MAGNETIC RESONANCE IN CHEMISTRY, VOL. 25, 331-334 (1987)

Steric Effects in the ^{17}O NMR Spectroscopy of Aromatic Methyl Ethers

M. A. Wysocki, P. W. Jardon, G. J. Mains and E. J. Eisenbraun*
Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74078, USA

D. W. Boykin*
Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, USA

^{17}O NMR spectroscopic data (natural abundance) were obtained for 19 methoxy-aromatic compounds: a series of substituted anisoles with a single *ortho* substituent, a series of 2, 6-disubstituted anisoles, a series of 3-substituted-1, 2-dimethoxybenzenes and three multi-substituted anisole derivatives. The chemical shifts of the highly hindered methoxy compounds are related to previously reported regiochemistry, spectroscopic results and from theoretical calculations for these compounds.

KEY WORDS ^{17}O NMR Aromatic methyl ethers Steric effects

INTRODUCTION

The influence of steric crowding on the properties of a variety of aromatic ethers has received considerable attention by several groups[1-6] and has important implications in explaining results ranging from regiospecificity of Lewis acid-catalysed cleavage of aromatic methoxy groups[1,6] to the autoxidation of biological molecules related to α-tocopherol.[5] In an earlier paper,[1] we showed that steric crowding (2,6-disubstitution with alkyl groups or a methoxy group and an alkyl group) of an aromatic methoxy group produces a significant deshielding of the ^{13}C NMR resonance of that group. In contrast, a single *ortho* substituent does not cause downfield shifts.[1,6] We also showed that steric crowding plays an important role in the regiochemistry of the Lewis acid-catalysed cleavage of aromatic methyl ethers to phenols. For example, iodotrimethylsilane cleaves 2,3-dimethoxytoluene exclusively to 2-methoxy-6-methylphenol.[6]

To explain these results, molecular orbital calculations (PRDDO),[1,7] ^{13}C NMR T_1 relaxation times of methoxy groups and ^{13}C NMR chemical shift measurements of the aromatic carbon atoms were performed.[1] PRDDO-MO calculations showed that the low-energy conformation of the carbon of a methoxy group having two *ortho* neighbours on a benzene ring is located out of the plane of the aromatic ring, whereas a methoxy group with only one *ortho* neighbor executes restricted rotation in the plane of the ring.[1] As expected, the carbon atom of the methoxy group is turned away from the neighboring substituent. Hence this methoxy group lies coplanar with the benzene ring in its most stable conformation, as has been reported for anisole.[1,2] These calculations also showed that the atomic charge on the oxygen atom in the former case exceeds that of the latter.[1] The carbon of a methoxy group with two *ortho* neighbors yields ^{13}C NMR T_1 relaxation times which are longer than those with only one *ortho* neighbor, also suggesting that the methoxy group with two *ortho* neighbors is crowded out of the plane of the aromatic ring.[1] ^{13}C NMR chemical shifts of the *ortho*-substituted methoxybenzenes did not correlate well with shifts predicted from published additive parameters,[8] further suggesting an unusual methoxy group orientation and distribution of electrons.[1,8]

We assume that the forced rotation of the methoxy group out of the plane of the aromatic ring diminishes the release of electrons from the methoxy group to the aromatic ring. The resulting increased atomic charge on the oxygen and the directed orientation of the oxygen orbitals facilitate complexation with Lewis acids and subsequent methoxy group cleavage.[1,6] This forced out-of-plane rotation influences the ^{13}C NMR chemical shifts of the methoxy carbons by creating an electronic imbalance in the methoxy group and enhancing the charge on oxygen. This provides a possible explanation for the deshielding of the ^{13}C NMR resonance of the crowded methoxy group and points to the need for ^{17}O NMR spectroscopic studies. A limited number of reports of ^{17}O NMR studies have appeared for aromatic ethers;[9-11] however, these did not deal with sterically crowded systems. Since the oxygen atom of the crowded methoxy group receives electron charge enhancement, the ^{17}O NMR resonance should be significantly shifted to higher field when compared with an uncrowded methoxy group. This shift was found in our study of the 19 methoxy-containing aromatic compounds shown in Tables 1 and 2.

EXPERIMENTAL

The measurements (at Oklahoma State University) were made with the ^{17}O nuclei at natural abundance (0.037%) on a Varian XL-300 spectrometer at 40.662 MHz in the FT mode. Samples were 60% v/v solutions in deuterated chloroform, in 5 mm tubes, at ambient temperature.

---

* Authors to whom correspondence should be addressed.

0749-1581/87/040331-04$05.00

Received 17 July 1986
Accepted (revised) 1 October 1986

The spectral settings were as follows: 25 kHz spectral width, 5000 data points, 16.5 or 20 μs pulse width, 0.1 second acquisition time with no acquisition delay, 500000 scans and 30 Hz line broadening. Chemical shifts are expressed in ppm relative to the oxygen of water when measured in a capillary tube placed concentrically within the sample tube.

The ^{17}O spectra were recorded (at Georgia State University) on a JEOL GX-270 spectrometer equipped with a 10 mm broad-band probe operating at 36.5 MHz. All spectra were acquired at natural abundance at 75 °C in dried acetonitrile containing 1% of butan-2-one as an internal standard. The concentration of the methoxy compounds employed in these experiments was 0.5 M. The signals were referenced to external deionized water at 75 °C. The butan-2-one resonance (558 ± 1 ppm) was used as an internal check on the chemical shift measurements for these compounds. The instrumental settings were spectral width 25 kHz, 2 K data points, 90° pulse angle (28 μs pulse width), 200 μs acquisition delay, 40 ms acquisition time and 40 000–100 000 scans. The spectra were recorded with sample spinning and without lock. The signal-to-noise ratio was improved by applying a 25 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. The reproducibility of the chemical shift data is estimated to be ±1.0.

Compounds **1–13**, **16** and **17** were available from previous work[1,6] or were commercially available. 3-Ethyl-1,2-dimethoxybenzene (**14**) and 3-isopropyl-1,2-dimethoxybenzene (**15**) were prepared as follows.

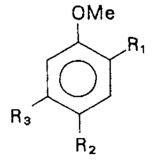
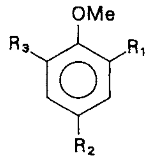
Preparation of 3-Ethyl-1,2-dimethoxybenzene (14)

A 7.0 g (0.039 mol) sample of 1-(2,3-dimethoxyphenyl)-ethanol, 1.4 g of 5% Pd/C and 60 ml of acetic acid were hydrogenated at 55 lb in^{-2} for 6 h. The mixture was cooled, filtered through Dicalite and concentrated. The concentrate was diluted with 400 ml of water and then extracted with diethyl ether three times. The combined ether extracts were washed with a solution of sodium hydrogen carbonate and separately with water, dried ($MgSO_4$), concentrated and Kugelrohr distilled to yield 5.25 g (90.8%) of **14** as a clear, colorless liquid; ^{1}H NMR ($CDCl_3$): δ 1.20 (t, 3, CH_3) and 6.68–6.94 (m, 3, ArH). ^{13}C NMR ($CDCl_3$): 152.08, 146.45, 137.17, 123.16, 120.60, 109.59, 59.70, 54.85, 22.60 and 14.67 ppm. Mass spectral data for $C_{10}H_{14}O_2$: *m/e* (M^+) 166.0990; found, 166.0994.

Preparation of 3-Isopropyl-1,2-dimethoxybenzene (15)

2-(2,3-Dimethoxylphenyl) propanol-2-ol (10.0 g; 0.05 mol) was treated with hydrogen in 75 ml of acetic acid, using 1.0 g of 10% Pd/C, at 55 lb in^{-2} for 6 h. The hydrogenolysed product was isolated, as described for **14**, to give 8.6 g (93.6%) of **15**. The product was further purified by Kugelrohr distillation. ^{1}H NMR ($CDCl_3$): δ 1.32 (d, 6, CH_3), 3.50 (m, 1, CH), 3.86 (s, 3, OCH_3), 3.92 (s, 3, OCH_3) and 6.80–7.14 (m, 3, ArH). ^{13}C NMR ($CDCl_3$): 152.10, 145.90, 141.56, 123.31, 117.56, 109.27, 59.79, 54.68, 26.24 and 22.83 ppm. Mass spectral data for $C_{11}H_{16}O_2$: *m/e* (M^+) 180.1146; found, 180.1139.

Table 1. ^{17}O NMR chemical shifts of methoxy groups of substituted anisoles

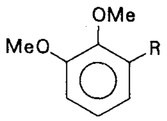
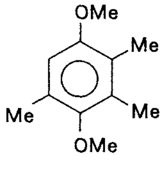
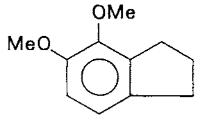
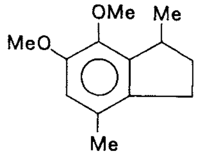
Compound		R_1	R_2	R_3	δ (ppm)[a]
1		H	H	H	48.0[b]
2		Me	H	H	46.2[b]
3		*t*-Bu	H	H	48.8[b](49.0)[c]
4		*t*-Bu	H	Me	48.0[c]
5		OMe	H	H	33.5[b]
6		H	OMe	H	40.0[c]
7		Me	H	Me	16.5[b]
8		Et	H	Et	16.7[b]
9		*i*-Pr	H	*i*-Pr	13.5[b]
10		*t*-Bu	H	*t*-Bu	27.3(29.6)[c]
11		*t*-Bu	H	Me	27.0[c]
12		*t*-Bu	Me	Me	24.3[c]

[a] Relative to water.
[b] Measured in 60% v/v $CDCl_3$.
[c] Measured on 0.5 M solutions in acetonitrile at 75 °C.

RESULTS AND DISCUSSION

The ^{17}O NMR chemical shifts are presented in Tables 1 and 2. As predicted from the previous arguments, the

Table 2. ^{17}O NMR chemical shifts of methoxy groups of substituted dimethoxybenzenes

			^{17}O chemical shift (ppm)[a]	
	Compound	R	One *ortho* neighbor[b]	Two *ortho* neighbors[c]
5		H	33.5	Absent
13		Me	36.4	10.5
14		Et	35.8	9.4
15		*i*-Pr	36.1	8.7
16		OMe	37.1	−6.1
17		—	40.7	9.8
18		—	27.2	12.6
19		—	26.8	7.6

[a] Relative to water (ppm).
[b] Refers to outside, unhindered methoxy group.
[c] Refers to methoxy group with two *ortho* substituents.

^{17}O signals of crowded methoxy groups (two *ortho* neighbors) are shifted upfield from the ^{17}O signals of uncrowded (one ortho neighbor) methoxy groups. These data support the earlier conclusions[1] explaining the selective cleavage of crowded as compared with uncrowded methoxy groups, and the downfield shifts of the methoxy ^{13}C NMR resonance. The interpretation of the ^{17}O results for these multi-substituted methoxybenzenes is complicated by a highly complex set of competing effects, including repulsive and attractive van der Waals interactions,[12] electronic effects of substituents and steric interactions which lead to both increased van der Waals interactions and to steric inhibition of resonance. At present, as a consequence of these interacting effects, it is possible only to point to very general qualitative trends; care is taken to avoid overinterpretation of the data.

The ^{17}O chemical shifts of anisole (**1**) and 4-methoxyanisole (**6**), both of which are assumed to be free from steric influences, are considered first. The chemical shift of **6** is upfield of that of **1** by 8 ppm (consistent with earlier results[9]). This shielding effect has been explained in terms of the electron-donating effect (electronic effect) of the second methoxy group.[9] In a study of the influence of electronic factors (electron-donating and withdrawing effects) on the chemical shifts of 4-substituted anisoles, Katoh *et al.*[9] found that the chemical shifts of these anisoles were correlated with the charge density and bond order matrix term of the Karplus–Pople relationship; a correlation with the ΔE term, which has been observed for aliphatic ethers,[10] was not found. Similar conclusions were drawn in a more recent study[11] of several different aromatic ether systems. The ^{17}O chemical shift 1,2-dimethoxybenzene (**5**), which is electronically equivalent (*ortho–para* equivalence) with **6**, is at 33.5 ppm, reflecting the effect of both electronic and steric interactions. The chemical shift difference between **5** and **6** is 6.5 ppm and is attributed to rotation of the methoxy group from its preferred conformation involving p-orbital overlap with the aromatic system. Rotation of the methoxy group which would decrease orbital overlap would be expected to increase single bond character on the oxygen, which is consistent with the observed upfield shift of the ^{17}O resonance of **5**. Introduction of an alkyl group at position 2 of anisole causes a much smaller shift (1.8 ppm) than the introduction of a methoxy group at position 2 (compare **1** with **2** and **5**). Presumably, the 8 ppm difference between **1** and **5** is the result of electronic factors (see above); hence the shift difference comparison to be made between **2** and **5** is between 6.5 and 1.8 ppm. The major conclusion to be drawn from this result is that the rotation of the methoxy group from the plane of the aromatic ring is greater for **5** than **2**, consistent with expected repulsion between the electrons on both oxygen atoms in **5**.[1,2,8] Consequently, comparison of the ^{17}O NMR chemical shifts of **1** and **5** suggests that two standards should be used. Anisole (**1**) and the remaining monalkyl derivatives belong in one group with their ^{17}O NMR resonance appearing at approximately 48 ppm, and 1,2-dimethoxybenzene (**5**), which exhibits a ^{17}O signal at 33.5 ppm, belongs in another group. Hence compounds with vicinal dimethoxy groups should be referred to **5** rather than to 1.

The ^{17}O NMR resonances for the more highly hindered substituted anisoles (containing at least one *ortho-tert*-butyl group) **10–12** (27.3, 27.0 and 24.3 ppm, respectively) are contrasted with those of **7**, **8** and **9** with the smaller 2,6-dimethyl, 2,6-diethyl and 2,6-diisopropyl groups which show resonances at 16.5, 16.7 and 13.5 ppm, respectively. One rationale for the trend in shifts is that when two groups are *ortho* to the methoxy group and one of them is a large group (*tert*-butyl), significant crowding results, giving rise to repulsive van der Waals interactions. Consequently, **10–12** are deshielded relative to **7–9**. Apparently, the presence of smaller groups in this configuration, as in **7–9**, allows conformations in which repulsive van der Waals interactions are not large. Bond angle deformation and/or deviations from planarity of the aromatic ring in these highly hindered molecules cannot at present be excluded as contributing to these shift differences.

The dimethoxybenzenes in Table 2 represent another interesting series of compounds which have large shifts for the two methoxy groups. The internal methoxy group is assigned the most upfield shift on the basis of higher estimated charge densities for the methoxy group rotated out of the plane of the ring.[1,2] The chemical shift values for the less hindered methoxy group of these compounds (**13–16**) is not significantly different from the value for **5**. The chemical shifts for the methoxy group with one *ortho* neighbor in **13–16** is remarkably consistent, suggesting that the most stable conformation for the methoxy group in question in these compounds is similar. The chemical shifts for the methoxy group with two neighbors in **13–15** are also essentially constant. Electronic factors become important in determining the chemical shift of the 2-methoxy group in 1,2,3-trimethoxybenzene (**16**); its shift is upfield by approximately 15 ppm compared with the analogous methoxy groups in **13–15**. This upfield shift is similar to that noted for 1,2-dimethoxybenzene (**5**) in comparison with **1–4**, again apparently reflecting rotation of the methoxy group from planarity as a result of the repulsive interactions of non-bonding electrons of the *ortho* methoxy groups. Hence the upfield shift reflects both electronic and conformational effects (see above).

The chemical shifts for the multi-substituted compounds **17–19** basically follow the patterns established by the simpler compounds previously described. The chemical shift of the 1-methoxy group in **17** is essentially the same as that for 1,4-dimethoxyanisole (**6**); the one *ortho* methyl group (position 2) and the other methyl groups have little influence on the chemical shift, as observed for the simple substituted anisoles **2–5**. The signal for the 4-methoxy group of **17** is as expected if one assumes that it is a composite of the shifts of **6** and **7**.

It is interesting that the chemical shifts of the hindered methoxy groups for the dimethoxyindanes **18** and **19** are changed relatively little from those noted for the analogous compounds **13** and **14**. In contrast, the shifts for the less hindered methoxy groups of **18** and **19** are shielded by 8–9 ppm compared with their counterparts in **13** and **14**. These shifts suggest a more non-planar conformation than that indicated for **13–15**.

The ^{17}O NMR chemical shifts of these substituted anisoles are qualitatively explained in terms of electronic factors and conformational changes arising from steric interactions; the shifts of highly hindered anisoles apparently also have contributions from repulsive van der Waals interactions and/or bond angle deformations. Qualitatively, the ^{17}O chemical shifts of these variously hindered anisoles are consistent with their previously reported physical data (x-ray, ionization potentials, ^{13}C NMR), regiochemistry and results from theoretical calculations.[1,2] The ^{17}O chemical shifts are considerably more sensitive to deviations in conformation of the methoxy groups as a function of structural variations than are the ^{13}C NMR data for these compounds. Consequently, ^{17}O NMR spectroscopy can serve as a sensitive probe for detection of solution phase conformation changes for aromatic methoxy groups.

Acknowledgements

Acknowledgement is made (by D.W.B.) to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

REFERENCES

1. P. W. Jardon, E. H. Vickery, L. F. Pahler, N. Pourahmady, G. J. Mains and E. J. Eisenbraun, *J. Org. Chem.* **49**, 2130 (1984).
2. G. M. Anderson, P. A. Kollman, L. N. Domelsmith and K. N. Houk, *J. Am. Chem. Soc.* **101**, 2344 (1979).
3. R. H. Contreras, M. B. Ferraro, D. G. de Kowalewski and L. Diaz, *Magn. Reson. Chem.* **23**, 296 (1985).
4. (a) S. R. Salman, *Magn. Reson. Chem.* **23**, 120 (1985); (b) S. R. Salman, *Spectrochim. Acta, Part A* **40a**, 229 (1984).
5. G. W. Burton, T. Doba, E. J. Gabe, L. Hughes, F. L. Lee, L. Prasad and K. U. Ingold, *J. Am. Chem. Soc.* **107**, 7053 (1985).
6. E. H. Vickery, L. F. Pahler and E. J. Eisenbraun, *J. Org. Chem.* **44**, 4444 (1979).
7. (a) T. A. Halgren and W. N. Lipscomb, *Proc. Natl. Acad. Sci. U.S.A.* **69**, 652 (1972); (b) T. A. Halgren and W. N. Lipscomb, *J. Chem. Phys.* **58**, 1569 (1973); (c) M. K. Eberhardt and G. Chuchani, *J. Org. Chem.* **37**, 3654 (1972).
8. K. S. Dhami and J. B. Stothers, *Can. J. Chem.* **44**, 2855 (1966).
9. M. Katoh, T. Sugawara, Y. Kawada and H. Iwamura, *Bull. Chem. Soc. Jpn.* **52**, 3475 (1977).
10. (a) T. Sugawara, Y. Kawada and H. Iwamura, *Bull. Chem. Soc. Jpn.* **52**, 3391 (1979); (b) C. Delseth and J.-P. Kintzinger, *Helv. Chim. Acta* **61**, 1327 (1978).
11. G. A. Kalabin, D. F. Kushnarev, R. B. Valeyev, B. A. Trofimov and M. A. Fedotov, *Org. Magn. Reson.* **18**, 1, (1982).
12. (a) S. Li and D. B. Chesnut, *Magn. Reson. Chem.* **24**, 93 (1986); (b) S. Li and D. B. Chesnut, *Magn. Reson. Chem.* **23**, 625 (1985).