# <sup>13</sup>C and <sup>17</sup>O NMR Study of Methoxy Groups in Chlorinated Di- and Trimethoxybenzenes

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<sup>13</sup>C and <sup>17</sup>O NMR data [chemical shifts and <sup>1</sup>J(CH) values] for the methoxy groups in isomeric 1,2-, 1,3- and 1,4-dimethoxybenzenes, 1,2,3-trimethoxybenzenes and most of their chlorinated derivatives and some related brominated compounds were measured for CDCl<sub>3</sub> solutions. The <sup>17</sup>O NMR chemical shifts show up to 60 ppm dispersion. Comparison between the compounds with and without adjacent chlorine atoms (2,6-di- and 2,4,6-trisubstitution) also showed a clear methoxy carbon chemical shift change. The number and position of the chlorine atoms in the aromatic ring give small but observable effects on the <sup>17</sup>O NMR chemical shifts of the methoxy group if it is coplanar with the aromatic plane. Similarly, the degree and nature of the substitution have a minor effect (about 1 Hz) on the <sup>1</sup>J(CH) direct coupling values.

KEY WORDS <sup>13</sup>C NMR chemical shifts and coupling constants <sup>17</sup>ONMR chemical shifts Chlorinated dimethoxybenzenes Conformational analysis

# **INTRODUCTION**

<sup>17</sup>O NMR spectroscopy is an important method for examining a wide variety of structural problems, especially in the conformational analysis of some flexible systems. This subject was reviewed in a previous paper<sup>1</sup> and by Boykin and Baumstark.<sup>2</sup> Several papers have been published dealing with the <sup>17</sup>O NMR properties of aromatic ethers,<sup>3-6</sup> but they did not deal with sterically crowded systems. Later, however, some papers were published on the <sup>17</sup>O NMR spectroscopy of hindered ethers. The <sup>17</sup>O chemical shifts of variously hindered anisoles have been shown to be consistent with previously reported physical data (x-ray, ionization potentials, <sup>13</sup>C NMR), regiochemistry and results from theoretical calculations.<sup>7</sup> Duddeck *et al.*<sup>8</sup> reported the <sup>17</sup>O NMR properties of coumarins, furocoumarins and related compounds, including the data for anisole and 1,4-dimethoxybenzene. In continuation of our previous studies,<sup>1,9</sup> we now report both the <sup>17</sup>O NMR and <sup>13</sup>C NMR data for the methoxy groups of isomeric dimethoxybenzenes, 1,2,3-trimethoxybenzene, most of their chlorinated derivatives and some related brominated compounds. Some of these compounds are of great interest from an environmental chemistry viewpoint (see references in Ref. 1).

## EXPERIMENTAL

Chlorinated veratroles (1,2-dimethoxybenzenes) were prepared from the corresponding chlorocatechols

0749-1581/90/040315-03 \$05.00 © 1990 by John Wiley & Sons, Ltd. (benzene-1,2-diols),<sup>10</sup> achieving the methylation with iodomethane.<sup>11</sup> The same procedure was used for the methylation of chlorinated hydroquinones or 4methoxyphenols<sup>12</sup> to chlorinated 1,4-dimethoxybenzenes. The starting compounds, viz. 1,2-di-, 1,3-di-, 1,4di- and 1,2,3-trihydroxybenzenes, tetrabromocatechol and 5-chloro-1,3-dimethoxybenzene were commercially available. 4,5-Dibromocatechol was prepared by bromination of catechol in CCl<sub>4</sub> solution and then methylated to 4,5-dibromoveratrole as discussed above. Chlorinated 1,2,3-trimethoxybenzenes were synthesized, using the above methylation procedure, from the corresponding chlorinated syringols (2,6-dimethoxyphenols), which were prepared by chlorination of 2,6-dimethoxyphenol.

The <sup>17</sup>O NMR investigations were carried out at natural abundance (0.037%) on a Jeol GSX-270 spectrometer at 36.5 MHz in the FT mode at 40 °C in a 10-mm NMR tube equipped with a coaxially inserted  $D_2O$  capillary tube used as an external reference. The samples were 0.25 M solutions in CDCl<sub>3</sub>. The digital resolution was 0.25 ppm and the accuracy of the <sup>17</sup>O NMR chemical shifts was about 0.5 ppm. Other recording conditions were the same as previously.<sup>1</sup> The methoxy carbon chemical shifts (referred to the central line of the solvent = 77.7 ppm) and the direct <sup>1</sup>J(CH) coupling constants were obtained from the same samples (CDCl<sub>3</sub>) and on the same spectrometer at 67.8 MHz at 30 °C. The digital resolution was better than 0.25 Hz.

### **RESULTS AND DISCUSSION**

The methoxy carbon chemical shifts, the direct  ${}^{1}J(CH)$ 

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		Chemical shift	ts (δ, ppm)						
	<sup>13</sup> C NMR <sup>b</sup>		170 NMR <sup>e</sup>		<sup>1</sup> J(CH) (Hz)				
			Pos	ition					
Compound®	1-	2-	1-	2-	1-	2-			
1,2-Dimethoxybenzene (DMB)	56.5	56.5	38.9	38.9	144.0	144.0			
3-	56.8	61.3	46.1	13 <sup>d</sup>	144.5	145.0			
4-	56.7	56.7	43.2	43.2	144.5	144.5			
3,4-	57.0	61.4	44.7	22ª	144.8	145.3			
3,5-	57.0	61.4	50.0	15 <sup>d</sup>	145.0	145.3			
3,6-	61.7	61.7	23.7	23.7	145.5	145.5			
4,5-	57.0	57.0	42.0	42.0	145.0	145.0			
3,4,5-	57.1	61.5	48.3	23ª	145.1	145.7			
3,4,6-	61.8°	61.9°	27.1	27.1	145.9	146.0			
3,4,5,6-	61.9	61.9	29.0	29.0	146.1	146.1			
4,5-Dibromo-			45.2	45.2					
Tetrabromo-	61.6	61.6	40.1	40.1	146.2	146.2			
3-Methyl-5-chloro-	56.6	60.9	45.9	10 <sup>d</sup>	144.4	144.1			
			Pos	sition					
	1-	3-	1-	3-	1-	3-			
1,3-Dimethoxybenzene (DMB)	55.9	55.9	54.8	54.8	143.7	143.7			
5-	56.2	56.2	59.9	59.9	144.2	144.2			
			Po	sition					
	1-	4-	1-	4-	1-	4-			
1.4-Dimethoxybenzene (DMB)	55.4	55.4	43.0	43.0	143.3	143.3			
2-	57.5	56.5	46.4	46.4	144.2	143.7			
2.3-	57.5	57.5	50.0	50.0	144.7	144.7			
2,5-	57.6	57.6	47.6	47.6	144.8	144.8			
2,6-	61.5	56.6	57.2	23ª	145.3	144.5			
2,3,5-	57.5	61.5	57	26ª	145.3	145.5			
2,3,5,6-	61.5	61.5	40.1	40.1	146.3	146.3			
					Position				
	1-	2-	3-	1-	2-	3-	1-	2-	3-
1,2,3-Trimethoxybenzene (TMB)	56.8	61.5	56.8	39.1	-1.2	39.1	144.1	144.4	144 1
4.6-	61.9	62.1	61.9	22.5	22.5	22.5	145.4	145.7	145.4
4,5,6-	62.0	62.2	62.0	24.9	24.9	24.9	145.7	145.7	145.7

# Table 1. <sup>17</sup>O and <sup>13</sup>C NMR data for methoxy groups in chlorinated methoxybenzenes

<sup>a</sup> The number indicate chlorinated positions.

<sup>b</sup> Referred to the central line of CDCl<sub>3</sub> (77.7 ppm from TMS).

° Referred to D<sub>2</sub>O.

<sup>d</sup> Very broad peak observed.

<sup>e</sup> Assignments may be reversed.

coupling-constants and the <sup>17</sup>O NMR data of the compounds are given in Table 1.

### Methoxy carbon chemical shifts and ${}^{1}J(CH)$ values

As we reported earlier<sup>9</sup> for chlorinated anisoles (methoxybenzenes) and guaiacols (2-methoxyphenols), the most important effects on the methoxy carbon chemical shifts are due to the chlorine atoms or/and methoxy groups adjacent to the methoxy substituents. For example, for a non-symmetric compound such as 3-chloroveratrole, the chemical shifts of methoxy carbons 1 and 2 are 56.8 and 61.3 ppm, respectively. This difference is due to the different mutual orientation of the methoxy groups. The methoxy group at position 1 (O—C bond) is definitely in the aromatic plane, but the methoxy group at position 2 prefers a perpendicular position for steric reasons.

The conformer vs. chemical shift relationship stated above can be applied to the assignment of the methoxy carbon peaks in the spectra of compounds having two or more methoxy groups, as reported in this paper. However, we could not assign unambiguously in this manner the spectra of two of the compounds studied. First, both methoxy groups of 3,4,6-trichloro-1,2dimethoxybenzene have two adjacent substituents and the chemical shift values are very close (difference *ca*. 0.1 ppm). We therefore could not determine unambiguously their  ${}^{1}J(CH)$  values, which were also nearly equal.

Second, initially we could not assign the methoxy carbon chemical shifts of 2-chloro-1,4-dimethoxybenzene; these were eventually assigned by using the chemical shift values of 2-chloro- and 3-chloroanisole (56.3 and 55.8 ppm, respectively<sup>9</sup>). A chlorine atom adjacent to the methoxy group in chloroanisoles seems to increase the methoxy carbon chemical shift value.<sup>9</sup> Hence the value of 57.5 ppm for 2-chloro-1,4-DMB (see Table 1) corresponds to the methoxy carbon at position 1. This assignment, and also that of the spectrum of 3,4, 6-trichloroveratrole (see above), could be verified by recording the spectra of the compounds in which one of the two methoxy groups is replaced with a deuteriomethoxy group. However, these deuteriated model compounds are not yet available for examination.

As can be seen in Table 1, the <sup>1</sup>J(CH) values are of nearly the same magnitude. The positions of the chlorine atoms and the methoxy groups on the benzene ring therefore have only a small effects on <sup>1</sup>J(CH), the average effect being only about 1 Hz. The value seems to be highest (average value *ca.* 145.5 Hz) for methoxy carbons with adjacent substituents. Generally, the number of chlorine atoms seems to increase the value of <sup>1</sup>J(CH), the largest effect being found for chlorinated 1,4-dimethoxybenzenes. For example, the values for the 1-methoxy groups of 1,4-DMB, 2-chloro-1,4-DMB, 2,3dichloro-1,4-DMB and tetrachloro-1,4-DMB are 143.3, 144.2, 144.7 and 146.3 Hz, respectively.

### <sup>17</sup>O NMR chemical shifts

Our data for non-chlorinated compounds (anisole, 1,2-DMB, 1,3-DMB and 1,4-DMB) agree well with those reported previously. For these compounds we obtained the values 50.7 ppm<sup>1</sup> (49,<sup>3</sup> 50,<sup>4,8</sup> 48.0 ppm<sup>7</sup>), 38.9 ppm (33.5 ppm<sup>7</sup>), 54.8 ppm and 43.0 ppm (41,<sup>8</sup> 40 ppm<sup>7</sup>), respectively. Based on the above data, an adjacent methoxy group seems to cause the most important effect on the <sup>17</sup>O chemical shifts of the methoxy groups. The chemical shift difference between 1,2-DMB and 1,4-DMB is 4.1 ppm (6.5 ppm<sup>7</sup>). This is attributed to rotation of the methoxy group from its preferred conformation involving p-orbital overlap with the aromatic system.<sup>7</sup>

Our previous study<sup>1</sup> showed that the range of the <sup>17</sup>O NMR shifts of anisole and its chlorinated derivatives is about 40 ppm. For the non-hindered methoxy compounds used in this investigation the smallest and the highest values are 38.9 ppm (for 1,2-DMB) and 59.9 ppm (for 5-Cl-1,3-DMB). The corresponding values for the hindered methoxy groups were about -1.2 ppm (referred to external D<sub>2</sub>O) and 29 ppm, respectively. This *ca.* 60 ppm range is probably due to the steric inhibition of the resonance between the aromatic ring and the oxygen lone pairs and the inductive effects caused by the electronegative chlorine substituents. The highest value (40.1 ppm) of the sterically hindered methoxy groups was observed for tetrabromoveratrole, which is more than 10 ppm higher than that of the corresponding value of tetrachloroveratrole (29 ppm). This difference is probably due to the different inductive effects in these compounds.

### CONCLUSIONS

The <sup>13</sup>C NMR chemical shifts of the methoxy groups in aromatic ethers are sensitive to the conformational changes due to steric crowding. This may be of great importance in predicting the biological and physiological structure-activity relationships of these compounds. The <sup>17</sup>O NMR chemical shifts also seem to obey the same relationship, and are therefore useful in the conformational analysis of aromatic ethers. Further, the <sup>17</sup>O chemical shift range of the compounds studied is very large, offering an opportunity for the statistical treatment of NMR data to establish the most important contributions to the <sup>17</sup>O NMR chemical shifts. This work is in progress.

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