

# Conformations of Highly Hindered Aryl Ethers—XVII

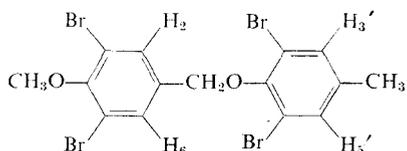
## Hindered Rotation and Carbon–Halogen Bond Magnetic Anisotropy in Benzyl Phenyl Ethers\*†

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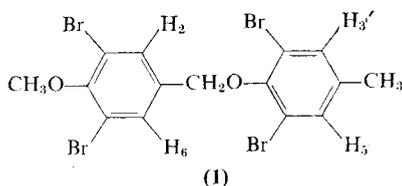
**Abstract**—The PMR spectrum of 3,5-dibromo-4-methoxybenzyl 2',6'-dibromo-4'-methylphenyl ether shows two aromatic proton



signals at  $\delta = 7.33$  and  $7.71$ . Comparison with related benzyl ethers and anisoles led to assignment of the upfield signal to the phenyl-ring protons ( $H_{3'}$  and  $H_{5'}$ ) and the downfield signal to the benzylic aromatic protons ( $H_2$  and  $H_6$ ). In view of the nearly identical inductive effects to which they are subjected, their large shift difference must be due to long-range effects in preferred conformations. Analysis showed that the anomalous shift observed for the benzylic aromatic protons is due to deshielding by both the other aromatic ring and by the carbon-halogen bonds. The relation of this work to related biphenyls and diphenyl ethers is discussed.

### INTRODUCTION

THE PREVIOUS part of this series<sup>1</sup> described the isolation and structure elucidation of 3,5-dibromo-4-methoxybenzyl 2',6'-dibromo-4'-methylphenyl ether (1):



Its PMR spectrum, which showed the five expected singlets (Table 1), was surprising on account of the large shift difference (0.38 ppm) observed for the two sets of aromatic protons ( $H_2$ ,  $H_6$  and  $H_{3'}$ ,  $H_{5'}$ ). In view of the nearly identical inductive effects to which they are subject (each has *ortho* to it a bromine and an alkyl group, *meta* to it an ether group and *para* to it another bromine), the shift difference must be due to long-range effects, which are analyzed here.

### RESULTS AND DISCUSSIONS

#### Reference Compounds

For comparison with 1, the related benzyl ethers (2 to 5) and anisoles (6 to 8) were prepared and their PMR spectra determined (Table 1).

#### PMR Assignments

From a comparison of 1 with 2 and 6, it is possible to assign to the phenyl aromatic protons the signal at 7.33 and to the benzyl aromatic protons that at the anomalously low field of 7.71. A similar deshielding of the corresponding protons in 2 to 5 also appears to be present,

\* A summary of this work was presented at the VII Mexican Congress of Pure and Applied Chemistry held in Morelia, Michoacán, 12th to 15th April 1972.

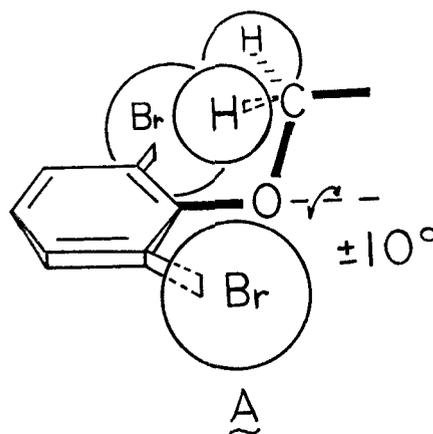
† For Part XVI, see Ref. 1.

but could not be ascertained on account of the complex spin-spin interactions. (In benzyl 4'-hydroxyphenyl ether they appear‡ at 7.38 and in benzyl 3'-methyl-4'-nitrophenyl ether<sup>2</sup> at 7.30 in  $CCl_4$ .)

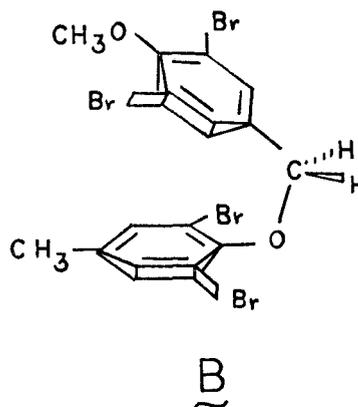
The shifts for the oxymethylene bridge and methoxy protons showed significant variations discussed below. All other signals appeared at normal positions.

#### Conformation of 1

Inspection of space-filling molecular models (Fischer-Taylor-Hirschfelder) shows that rotation about the ether linkage is severely restricted due to steric interference between the bromines *ortho* to it and the methylene group, forcing the latter to adopt the *peri*-planar positions with an estimated libration of only  $\pm 10^\circ$  about the  $C1'-O$  bond (A):



Rotation about the  $O-CH_2$  bond is somewhat freer, but also restricted by steric interference between the bromines and the benzylic aromatic protons. Concerted rotation about both ether bonds could lead to the folded conformation (B):



‡ Obtained by determining the spectrum of the commercially available product under the conditions given in Table 1.

TABLE I. PMR OF ARYL BENZYL AND METHYL ETHERS<sup>a</sup>

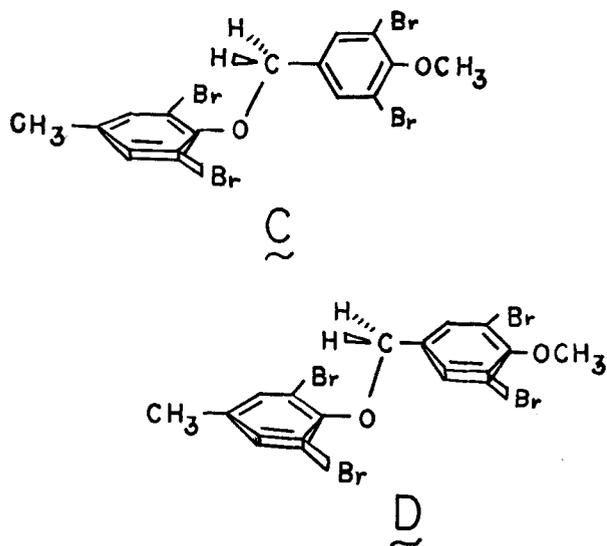
Compound	4'-CH <sub>3</sub>	CH <sub>3</sub> O—	—CH <sub>2</sub> O—	3',5'-H	2,6-H	Other
(1)	2.30	3.88	4.88	7.33	7.71	—
(2)	2.26	—	5.00	7.35	7.20 to 7.76 <sup>b</sup>	—
(3)	2.25	—	4.98	7.65	7.16 to 7.83 <sup>b</sup>	—
(4)	2.25	—	5.46	7.63	7.33 to 8.49 <sup>b</sup>	—
(5)	2.23	—	4.75	6.81	7.16 to 7.58 <sup>b</sup>	2',4',6'-Me <sub>3</sub> = 2.23
(6)	2.25	3.83	—	7.31	—	—
(7)	2.21	3.80	—	7.53	—	—
(8)	2.25	3.70	—	6.83	—	2,4,6-Me <sub>3</sub> = 2.25

<sup>a</sup> Chemical shift ( $\delta$ ) in ppm downfield from internal TMS in *ca.* 10% w/v solutions in CDCl<sub>3</sub> at 60 MHz.

<sup>b</sup> Complex multiplet spanning the range indicated.

Although it is unstrained and there are no unusually close approaches, it is an improbable conformation because: (a) the mutual shielding of the aromatic protons expected in this conformation is not observed and (b) dipole-dipole repulsions occur between the carbon-bromine bonds.\*

Finally, rotation about the  $\text{CH}_2\text{—Cl}$  bond is completely free since there are no steric or conjugative restrictions. This allows the benzylic aromatic ring (and its substituents) to occupy all the positions to which it is taken by rotation about this bond (e.g. **C** and **D**):



It will be noted that in all such rotamers (e.g. **C** and **D**) the benzylic aromatic protons are always found close to the other aromatic ring and near its plane and thus are exposed to the deshielding caused by its magnetic anisotropy.

A detailed geometrical analysis (see Appendix) located these protons in relation to the center of the phenyl ring. By use of the deshielding values given by Johnson and Bovey,<sup>4</sup> their estimated shifts were determined. These are 0.21 and 0.00 for the proximal and distal protons in **C**, and 0.14 ppm for those in **D**. Thus the estimated deshielding caused by the phenyl ring anisotropy, is at best only half the observed value.

#### C—Br Bond Magnetic Anisotropy<sup>5</sup>

The remaining deshielding is attributed to the diamagnetic shift arising from the magnetic anisotropy of the carbon-halogen bonds. This is shown by a comparison of the chemical shifts of the benzyl aromatic protons of **2** and **3** with those of **5**: in the latter the multiplet is centered about 0.2 ppm to higher field than in **2** and **3**. Since in all three cases the steric situation is similar, the difference can only be due to the presence or absence of halogens.

In most of the examples of C—X bond anisotropy described previously,<sup>6</sup> direct effects due to the halogens (which are often in the opposite sense) have made its exact delineation difficult. In the present case, however, these may be considered to be absent since the orthogonal disposition of the *p* orbitals on  $\text{Cl}'$  and O is an

\* A similar folded conformation has been suggested for benzyl diketopiperazine derivatives, and its stabilization ascribed to an attractive  $\pi\text{—}\pi$  interaction between the  $\pi$  electrons and the amide bonds.<sup>3</sup>

efficient barrier to their mesomeric transmission, while the seven intervening bonds (including a methylene bridge) annul any inductive effects. Fortunately also, in this case the aromatic ring and C—X bond deshieldings are effective in the same sense, simplifying their factorization.

By contrast, the downfield shift attributable to the anisotropy of the two C—Br bonds is estimated to be between 0.2 and 0.3 ppm in **1**. This would seem to be a reasonable estimate in view of the remaining conformational mobility which results in large distances (ca. 4.0 to 4.3 Å) from the C—Br bond midpoint to the closest protons in **C** and **D** (see Appendix).

#### Methylene Protons

In conformations **C** and **D** the methylene protons are located only 3.0 Å from the nearest C—Br bond midpoint and should also reflect these effects. In two analogous unhindered ethers (benzyl 4'-hydroxyphenyl<sup>†</sup> and benzyl 3'-methyl-4'-nitrophenylethers<sup>2</sup>) the methylene protons occur at 5.00 and 5.04 ppm. The near-absence of restraints to rotation about the  $\text{Cl}'\text{—O}$  bond results in a time-averaged positioning of these protons near the plane of the phenyl aromatic ring and their consequent deshielding.<sup>‡</sup> Upon introduction of steric restraint to rotation, as in **5**, their signal is shifted to 4.75 ppm, due to reduced deshielding in the *peri*-planar conformation by the trimethylphenyl ring. When the methyl groups of **5** are replaced by halogens, as in **2** and **3**, this effect is counterbalanced by the deshielding due to the carbon-halogen bonds, resulting in signals at 5.00 and 4.98 ppm, respectively. A parallel, but smaller effect is also apparent in the anisoles, where the methoxyl protons appear deshielded in the presence of *ortho* halogen substituents (**1**, **6**, **7**), but not when the *ortho* substituents are methyl groups (**8**)<sup>§</sup>. Since the methylene and methoxyl protons are closer to the C—Br bond midpoint and more nearly in its bisecting perpendicular plane than are the benzylic aromatic protons, they should experience stronger deshielding. Since equivalent shifts are observed for them, however, the presence of direct through-space shielding by the halogen atom electrons is surmised.

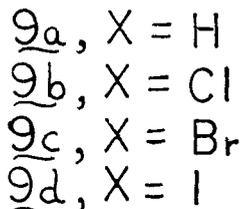
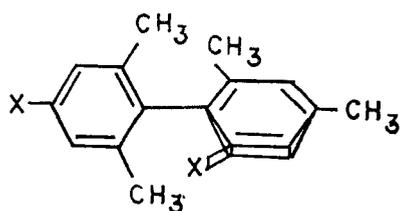
#### Relation to other Diaryl Systems

Although no other studies on benzyl aryl ethers of this type<sup>8</sup> have been reported, extensive work has been carried out on related biphenyls<sup>9</sup> and diphenyl ethers.<sup>10 to 17</sup> Nomura and Takeuchi specifically looked for carbon-halogen bond anisotropy effects in *ortho* substituted biphenyls (**9a** to **9d**), but found no evidence for them. This was surprising since the carbon-halogen bond midpoint to observed-proton distance (in the skew conformation<sup>10</sup>) is nearly identical at 3.6 Å. In fact the methyl protons in **9a** to **9c** appear uniformly at 1.91 and at slightly higher field (1.82 ppm) in **9d**. Although several explanations are possible, it is most likely that a combination of factors (increased libration

<sup>†</sup> Obtained by determining the spectrum of the commercially available product under the conditions given in Table 1.

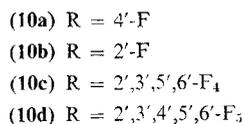
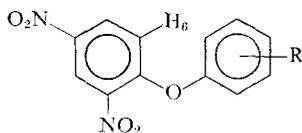
<sup>‡</sup> The conformationally rigid analog, 6*H*-dibenzo-[*b*, *d*]-pyran, although known,<sup>7</sup> was not available for comparison.

<sup>§</sup> Since direct inductive and mesomeric effects are strong in the anisoles, the observed trend may be fortuitous.

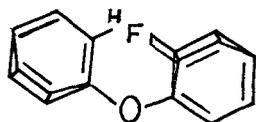


of the Cl—Cl' bond, closer location of the methyl group to the opposite aryl ring, counterbalancing direct effects of the halogens and interannular transmission of inductive effects) obscure evidence for C—X bond anisotropy.

The presence of a similar effect has recently been discovered in related fluoro diphenyl ethers.<sup>13</sup> The



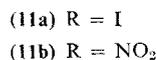
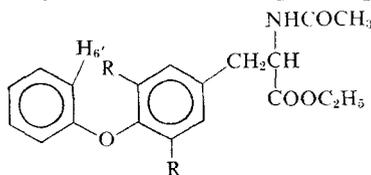
chemical shifts of the *ortho* proton on the dinitro-ring (H<sub>6</sub>) show that it is shielded relative to the corresponding anisole (7.25) due to the magnetic anisotropy of the other ring, but it appears at progressively lower fields on going from no *o*-fluorines (10a, 7.01), to one (10b, 7.05) and to two (10c, 7.13 and 10d, 7.12). This effect is attributed to deshielding by the C—F bonds in the *endo*-fluoro twist conformations E:



E

A similar effect can be deduced from the data given by Montaudo *et al.*<sup>16</sup> for ethers and thioethers where replacement of an *ortho* methyl substituent by chlorine leads to deshielded values on the other ring.

In an earlier PMR study of ethers related to thyroxine<sup>10</sup> it was seen that H<sub>6'</sub> is found consistently upfield in 2,6-diiodophenyl ethers (11a, average 6.07) relative to 2,6-dinitrophenyl ethers (11b, average 6.22 ppm):

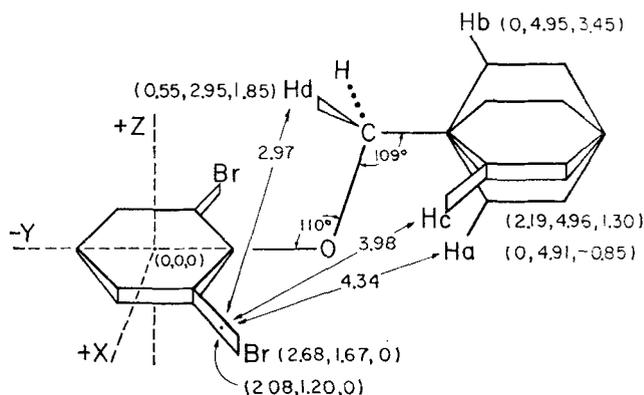


In view of more recent work<sup>11 to 15</sup> and the present findings, it is apparent that the shieldings observed for H<sub>6'</sub> relative to benzene protons (11a, average 1.30 and 11b, average 1.15 ppm) are the result of many effects, including deshielding by the C—I bonds.<sup>18</sup>

## APPENDIX

### Geometrical Analysis and Predicted Shielding Values

Using the bond lengths C<sub>ar</sub>—C<sub>ar</sub> = 1.40, C<sub>ar</sub>—CH<sub>2</sub> = 1.51, C<sub>ar</sub>—O = 1.39, CH<sub>2</sub>—O = 1.42, C<sub>ar</sub>—Br = 1.89 and C<sub>ar</sub>—H = C(H)—H = 1.09 Å, and the valency angles C<sub>ar</sub>—CH<sub>2</sub>—O = 109°, C<sub>ar</sub>—O—CH<sub>2</sub> = 110°, C<sub>ar</sub>—C<sub>ar</sub>—Br = C<sub>ar</sub>—C<sub>ar</sub>—H = 120°, basal and elevation projections were made graphically using 1 Å = 4 cm, with the coordinate system originating at the center of the phenyl ring. From these the following coordinates were obtained (*x*, *y*, *z* in Å) for the pertinent points (Scheme 1).



SCHEME 1. Location of pertinent protons in relation to the center of the positioning ring (*x*, *y*, *z* in Å) and their distance from the C—Br bond midpoint (in Å).

The corresponding *z*,  $\rho$  coordinates<sup>4</sup> and predicted deshielding values (ppm) are: Ha(0.61, 3.54) = 0.208; Hb(2.48, 3.56) = 0.002; Hc(0.94, 3.86) = 0.135; Hd(1.33, 2.16) = 0.143. As determined analytically from the coordinates, the C—Br midpoint to proton distances are 3.98 Å for Hc, 4.34 Å for Ha and 2.97 Å to Hd. The distance from the closest bromine to Ha is 4.25 Å, to Hc is 3.53 Å and to Hd is 3.10 Å.

## EXPERIMENTAL

**2,6-Dibromo-4-methylphenyl benzyl ether (2).**<sup>19</sup> To a solution of the phenol<sup>1</sup> (1.8 g, 5 mmoles) in methyl ethyl ketone (50 ml) was added K<sub>2</sub>CO<sub>3</sub> (2.1 g, 15 mmoles) and heated to reflux. Benzyl chloride (1.9 g, 15 mmoles) was added in three portions over 1 hr. The mixture was refluxed a further 2 hrs., during which time its color changed from blue to purple and there was formed a precipitate of different appearance from that present originally (KCl). The reaction mixture was cooled and filtered, the precipitate washed with two portions of warm methyl ethyl ketone and the combined filtrates were taken to dryness under reduced pressure. The resulting solid was treated with warm ethanol and a few drops of water, with which it crystallized, having a slight brown color (1.2 g). It was recrystallized from aq. alcohol with activated charcoal treatment to give 900 mg (51%) of white crystals, m.p. 70 to 71° (Kofler). Found: %C, 47.31; %H, 3.44; %Br, 44.70; C<sub>14</sub>H<sub>12</sub>Br<sub>2</sub>O requires: %C, 47.23; %H, 3.40; %Br, 44.89.

**2,6-Diiodo-4-methylphenyl benzyl ether (3).** Prepared in the same way from the iodophenol<sup>20</sup> in 42% yield, m.p. 97 to 99° (Kofler). Found: %C, 37.52; %H, 2.61; %I, 56.21; C<sub>14</sub>H<sub>12</sub>I<sub>2</sub>O requires: %C, 37.36; %H, 2.69; %I, 56.40.

2,6-Diiodo-4-methylphenyl 1'-methyl-naphthyl ether (4). Prepared in the same way as 3 from 1-chloromethylnaphthalene. There was obtained a 49% yield of colorless crystals, m.p. 118 to 120°. Found: %C, 43.37; %H, 2.91; %I, 50.83; C<sub>18</sub>H<sub>14</sub>I<sub>2</sub>O requires: %C, 43.23; %H, 2.82; %I, 50.76.

2,4,6-Trimethylphenyl benzyl ether (5).<sup>21</sup> To 2,4,6-trimethylphenol (1.36 g, 0.01 mole) dissolved in 100 ml toluene was added 0.85 g of KOH and the mixture was heated under reflux with an attached Dean-Stark water separator under a current of N<sub>2</sub>. After no more water separated, the toluene was distilled off, and there was added 80 ml DMF, benzyl chloride (3.7 g, 0.03 mole), freshly prepared copper powder (100 mg) and copper acetate (100 mg). About 20 ml of the reaction mixture was distilled off to remove any remaining water, and heating under reflux and N<sub>2</sub> was continued for 4 hrs. After cooling there was added 25 ml conc. HCl and 60 ml MeOH and the mixture was poured onto 400 g ice. This was extracted four times with 80 ml portions of benzene, and the combined extracts were washed twice with 100 ml of 5% NaOH and twice with water. After treatment with activated charcoal and drying over Na<sub>2</sub>SO<sub>4</sub>, the solvent was removed under reduced pressure, leaving a slightly brown liquid (2.4 g). It was distilled under reduced pressure (109° at 1.53 Torr) to give a transparent, pleasant smelling liquid (1.15 g, 51%). Found: %C, 83.99; %H, 7.91; C<sub>16</sub>H<sub>18</sub>O requires: %C, 84.99, %H, 7.07.

Anisoles. The three known anisoles (6 to 8) were prepared by standard procedures to be reported elsewhere.

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