

## CONFORMATIONAL PREFERENCE OF ORTHO-SUBSTITUTED DIPHENYL ETHERS AND DIPHENYL THIOETHERS

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**Abstract**—NMR data are reported for two series of *ortho* substituted diphenyl ethers (DPO) and diphenyl thioethers (DPS). The results obtained indicate that in these molecules, in addition to steric hindrance effects, conjugative effects may prove important in determining conformational preferences.

THE conformational preferences of diphenyl ethers (DPO) and diphenyl thioethers (DPS) in solution have been investigated during the last three decades, mainly by dipole moment measurements,<sup>1-8</sup> but also by other techniques such as the Kerr constants<sup>9, 10</sup> and dielectric relaxation methods.<sup>5, 7, 11, 12</sup> All this data has not always resulted in unequivocal conformational assignments, and has left several problems unsolved.

We have extended our study on the conformational properties of substituted diphenylmethanes<sup>13, 14</sup> in solution to certain *ortho* substituted DPO and DPS in view of structural similarity between these systems. The conformational preference of tri-*ortho*-substituted DPO, elucidated by NMR,<sup>15, 16</sup> is similar to that found in diphenylmethanes,<sup>13, 14</sup> as expected owing to a similar molecular geometry in the two systems.

However, an important difference in these aromatic compounds arises from the fact that unshared electrons of the bridged heteroatom may develop a resonance interaction with the  $\pi$ -electrons of the aromatic ring.<sup>4, 7</sup> The intensity of this resonance effect and the extent to which it would affect the conformational preference of these molecules, proved an interesting subject of investigation.

Previously, anomalous NMR chemical shifts have been observed for some 2,4-dinitro-DPS.<sup>17</sup> These shifts, we believe, are due to conformational preference induced by a strong conjugative effect. This, however, was not completely realized by the previous workers,<sup>17</sup> since they attributed the effect only to the magnetic anisotropy of the aromatic ring, without considering the possibility of conformational preferences.

### RESULTS AND DISCUSSION

Tables 1 and 2 reported the NMR chemical shifts of *ortho* aromatic protons for a number of diphenyl ethers and diphenyl thioethers together with those of some reference anisoles and thioanisoles.

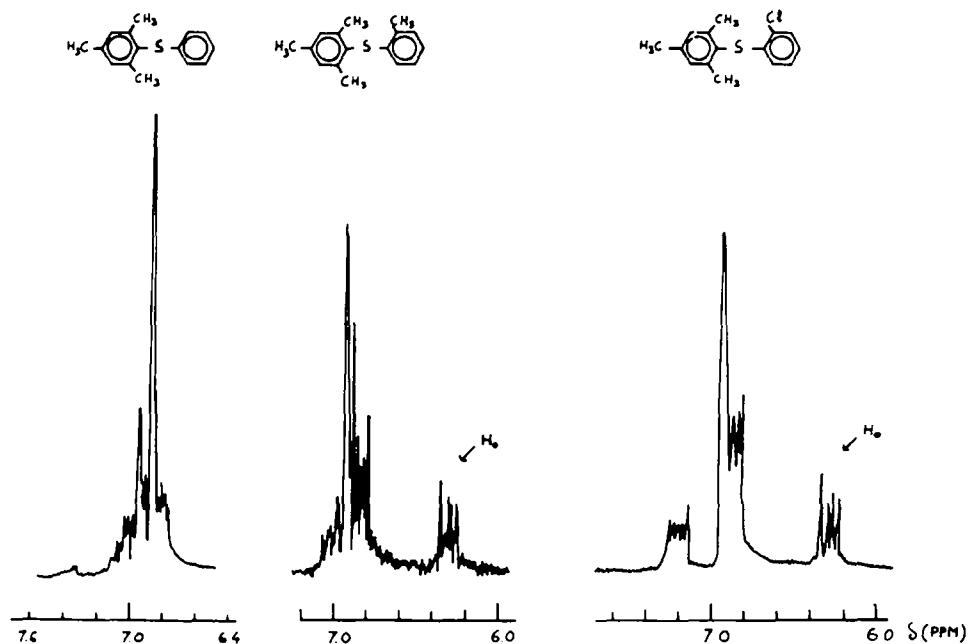


FIG 1. NMR spectra (aromatic region) of compounds 3, 4, 7 of Table 2. The label  $H_o$  denotes the peak due to the shielded *ortho* proton.

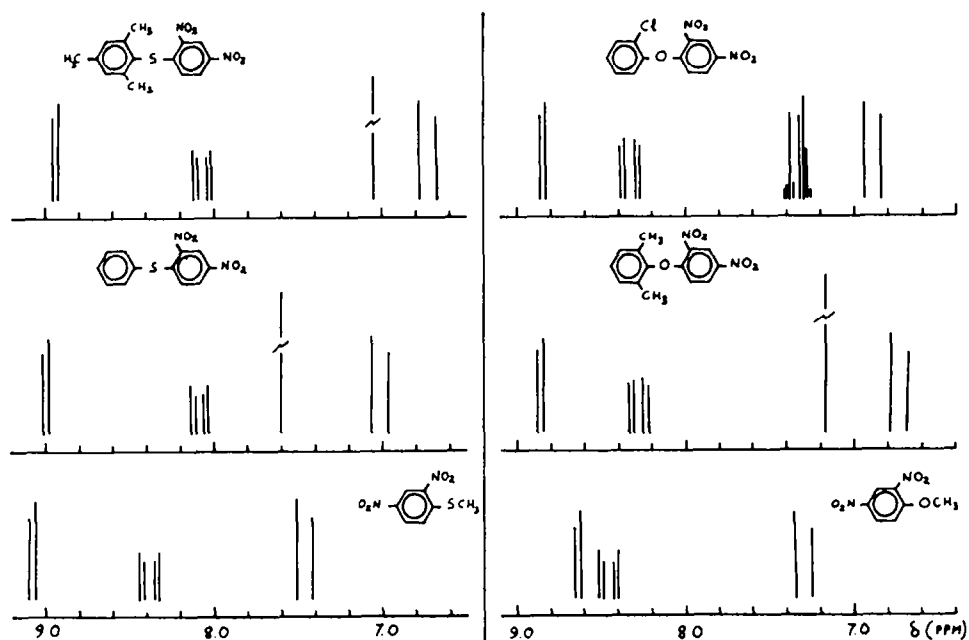
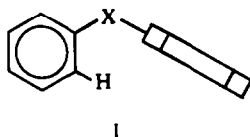


FIG 2. Schematic NMR spectra of aromatic protons.  $\delta$  (ppm) downfield from TMS in  $CDCl_3$  solution, at 100 MHz.

The chemical shifts of *ortho* nuclear protons vary considerably according to the substitution pattern present in the adjacent aromatic ring. This effect can be accounted for considering the diamagnetic shielding of the ring current<sup>18</sup> of the neighbouring aromatic nucleus on the *ortho* positions. Our previous work on diphenylmethanes<sup>13</sup> has shown that the magnitude of the diamagnetic shielding is related to the molecular conformation. In the present case, owing to the magnetic anisotropy of the bridged heteroatoms, the magnitude of the shielding due to the neighbouring aromatic nucleus cannot be computed simply from the difference between the chemical shifts of *ortho* and *para* nuclear protons. To correct for the magnetic anisotropy of the bridged heteroatoms the above shieldings were computed as the difference between the chemical shifts of DPO and those of the corresponding anisoles (Table 1, column 4), and between the chemical shifts of DPS and those of the corresponding thioanisoles (Table 2, column 4). In Fig 1 are reported some spectra relative to the region of the aromatic protons.

In the *ortho* tri-substituted derivatives (comps 11, Table 1 and 4, 7, 14, Table 2) the *ortho* nuclear hydrogens appear considerably diamagnetically shielded (0.6–0.8 ppm). This shielding suggests that these compounds exist preferentially in a form I where the *ortho* aromatic hydrogen lies below the adjacent ring.



This conformation is analogous to that described for the identically substituted diphenylmethanes,<sup>13</sup> and has also been proposed in the case of some thyroxine analogues.<sup>15</sup>

A theoretical shielding of about 1.10 ppm was calculated\* for the *ortho* aromatic proton lying below the adjacent ring (form I) in diphenyl ethers, and a shielding value of about 1.00 ppm was calculated\* in the case of diphenyl thioethers. The agreement in Tables 1 and 2 is better for diphenyl thioethers (about 0.7–0.8 ppm) than for diphenyl ethers (about 0.57 ppm). Torsional oscillations around the equilibrium dihedral angle may cause time-averaging of the signals,<sup>14</sup> and the oscillation amplitude may be different for the two classes of compounds.

Although a choice between completely free rotation or precisely one conformation (with torsional oscillation) may seem an over-simplification, this is not so in the present case.

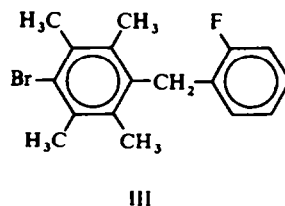
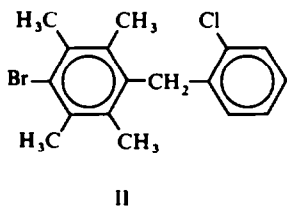
The potential energy surface, plotted as a function of the internal rotation angles for DPO, has been shown<sup>20</sup> to exhibit only one minimum. This minimum is surrounded by such large conformational barriers to be fairly described as *the* conformation.

In the case of diphenylmethanes (molecules so closely related to DPO that the potential energy surface is not expected to vary sensibly), compounds II and III were

\* Calculations were made assuming literature data<sup>19</sup> on the molecular geometry of these molecules. For each conformation the intramolecular distances were calculated in terms of  $\rho$  and  $z$  coordinates by standard trigonometric procedures. The shieldings in ppm for values of cylindrical coordinates were obtained from the Johnson and Bovey tables.<sup>18</sup>

Reference 15 p. 373 quote 2.5–3.0 ppm for an essentially identical calculation. This shielding value is manifestly too high, due presumably to some trivial computing mistake.

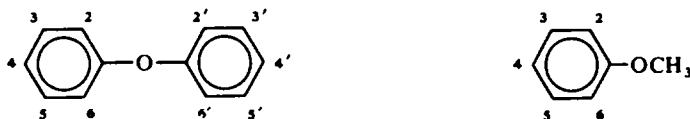
found<sup>21</sup> to have experimental dipole moments (1.25D and 1.29D, respectively) almost coincident with those calculated for these molecules in form I (1.43D and 1.37D, respectively).



It has been shown<sup>21</sup> that the dipole moment value, calculated as a function of the internal rotation angles, exhibits only one minimum which happens to be coincident with the conformational minimum (form I).

Data in Tables 1 and 2 also suggest a strong conformational preference (form I) for a number of 2,4-dinitro derivatives (comps 8, 9, 10, 11, Table 1 and 11, 12, 13, 14, Table

TABLE 1. CHEMICAL SHIFTS<sup>a</sup> OF *ortho* AROMATIC PROTONS IN CERTAIN DIPHENYLETHER AND ANISOL DERIVATIVES



No.		Chem. Shift H <sub>6'</sub>		Chem. Shift H <sub>6</sub>	Δ <sup>b</sup> (ppm)
1	2' CH <sub>3</sub>	6.75	2 CH <sub>3</sub>	6.66	-0.09
2	2,2' CH <sub>3</sub>	6.63			0.03
3	2,6 CH <sub>3</sub>	6.67			-0.01
4	2' Cl	6.92	2 Cl	6.80	-0.12
5	4' NO <sub>2</sub>	6.92	4 NO <sub>2</sub>	6.88	-0.04
6	2 CH <sub>3</sub> , 4' NO <sub>2</sub>	6.85			0.03
7	2 Cl, 4' NO <sub>2</sub>	6.84			0.04
8	2', 4' NO <sub>2</sub>	7.00	2, 4 NO <sub>2</sub>	7.30	0.30
9	2 CH <sub>3</sub> , 2', 4' NO <sub>2</sub>	6.86			0.44
10	2 Cl, 2', 4' NO <sub>2</sub>	6.90			0.40
11	2, 6 CH <sub>3</sub> , 2', 4' NO <sub>2</sub>	6.73			0.57
12	2' NO <sub>2</sub>	6.89	2 NO <sub>2</sub>	6.98	0.09
13	4' COCH <sub>3</sub>	6.93	4 COCH <sub>3</sub>	6.80	-0.13
14	4' NH <sub>2</sub>	6.73	4 NH <sub>2</sub>	6.60	-0.13
15	2' NH <sub>2</sub>	6.60	2 NH <sub>2</sub>	6.58	-0.02


<sup>a</sup> Chemical shifts measured in CDCl<sub>3</sub> at 30°, in ppm downfield from TMS as internal standard, at 100MHz.

<sup>b</sup> Δ = H<sub>6 Anisol</sub> - H<sub>6' Diphenylether</sub>: i.e., difference between chemical shifts of *ortho* aromatic protons of diphenylethers and those of the corresponding Anisols.

2). Remarkably, *ortho* substituents are not necessary to induce a conformational preference in these compounds, although the latter is more pronounced by their presence (Fig 2).

In the *ortho* tri-substituted compounds the preponderance of form I comes from the steric repulsion among *ortho* substituents which forces the molecule to assume the less hindered position. The driving force in the case of 2,4-dinitro derivatives results instead, from the conjugation of the heteroatoms with the phenyl ring. The process

TABLE 2. CHEMICAL SHIFTS<sup>a</sup> OF *ortho* AROMATIC PROTONS IN CERTAIN THIOANISOL AND DIPHENYLTHIOETHER DERIVATIVES



The image shows two chemical structures. The left structure is a diphenyl thioether, consisting of two benzene rings connected by a sulfur atom (S). The protons on each ring are numbered: 2 and 6 on the left ring, and 2' and 6' on the right ring. The right structure is thioanisole, which is a benzene ring with a methylsulfanyl group (-SCH<sub>3</sub>) attached. The protons on the ring are numbered 2 and 6.

No.		Chem. Shift H <sub>6</sub>		Chem. Shift H <sub>6</sub>	Δ <sup>b</sup> (ppm)
1	2' CH <sub>3</sub>	7.11	2 CH <sub>3</sub>	6.98	-0.13
2	2,2' CH <sub>3</sub>	6.98			0.00
3	2,4,6 CH <sub>3</sub>	6.87			0.11
4	2,4,6,2' CH <sub>3</sub>	6.21			0.77
5	2' Cl	6.94	2 Cl	7.02	0.08
6	2,2' Cl	7.10			-0.08
7	2,4,6,CH <sub>3</sub> ,2' Cl	6.28			0.74
8	4' NO <sub>2</sub>	7.10	4 NO <sub>2</sub>	7.21	0.11
9	2 CH <sub>3</sub> ,4' NO <sub>2</sub>	7.00			0.21
10	2 Cl,4' NO <sub>2</sub>	7.18			-0.03
11	2',4' NO <sub>2</sub>	6.93	2,4 NO <sub>2</sub>	7.51	0.58
12	2 CH <sub>3</sub> ,2',4' NO <sub>2</sub>	6.78			0.73
13	2 Cl,2',4' NO <sub>2</sub>	6.88			0.63
14	2,4,6 CH <sub>3</sub> ,2',4' NO <sub>2</sub>	6.72			0.79
15	2' NO <sub>2</sub>	6.82	2 NO <sub>2</sub>	7.30	0.48
16	2',2 NO <sub>2</sub>	7.30			0.00
17	4' COCH <sub>3</sub>	7.14	4 COCH <sub>3</sub>	7.13	-0.01
18	4' NH <sub>2</sub>	7.22	4 NH <sub>2</sub>	7.02	-0.20

<sup>a</sup> Chemical shifts measured in CDCl<sub>3</sub> at 30°, in ppm downfield from TMS as internal standard, at 100MHz.

<sup>b</sup> Δ = H<sub>6 Thioanisol</sub> - H<sub>6 Diphenylthioether</sub>: i.e., difference between chemical shifts of *ortho* aromatic protons of diphenylthioethers and those of the corresponding Thioanisols.

can be described as due to the concerted effect of the two strong electron-attracting groups, resulting in a partial bond arising between  $\pi$ -electrons localized on the bridgehead C atoms and the unshared electron pairs of the heteroatoms.<sup>19, 22, 23</sup> The high percentage of double bond character in the C<sub>Ar</sub>-X bond causes the aromatic ring bearing the two nitro groups to lie in the C<sub>Ar</sub>-X-C<sub>Ar</sub> plane. The steric repulsion

then forces the adjacent ring out of this plane, so that the molecule assumes the conformation I. If the adjacent ring carries *ortho* substituents the process will be favoured and the conformational preference will be enhanced.

In the case of 2-nitrodiphenyl thioether (compd. 15, Table 2), the magnitude of the shielding effect (0.48 ppm) suggests that the 2-nitro derivative exists preferentially in form I.

Other substituents reported in Table 1 and 2, 2-CH<sub>3</sub>, 2-Cl, 4-COCH<sub>3</sub>, 4-NH<sub>2</sub>, 4-NO<sub>2</sub>, fail to show conjugative effects strong enough to induce conformational preferences in these molecules.

The importance of conjugative effects in determining conformational preferences in DPO and DPS has been neglected in previous NMR investigations.<sup>17, 22, 24, -27</sup>

The dipole moment of diphenyl ethers have been recently reviewed<sup>7</sup> and the experimental values have been compared with those calculated for the internal free rotation in these molecules. The agreement between calculated and experimental values has been taken as indicating the absence of large conjugative effects in these molecules.<sup>5</sup>

It is, however, not always safe to draw conclusions from such analyses. For instance, the experimental<sup>4</sup> value for 2-nitrodiphenyl thioether (5.22D) agrees fairly well with the calculated\* one for the free internal rotation (4.48D), but NMR data (Table 2) suggest that this compound exists preferentially in form I and the dipole moment value calculated for this conformation is 5.20D, almost coincident with the experimental value. Moreover, in the case of 2,4-dinitrodiphenyl thioether the dipole moment values calculated for the molecule in form I and for the free rotating molecule nearly coincide (about 4.0D).

The difficulties involved in the interpretation of dipole moment data of molecules of this (angular) type have been discussed previously.<sup>14</sup> The NMR data presented here provide evidence that both steric and conjugative effects may induce conformational preferences in these molecules.

#### EXPERIMENTAL

The methods of preparation and the complete NMR peak assignments for the compounds discussed in this paper will be reported elsewhere.<sup>28</sup> Chemical shifts values reported in Tables 1 and 2 are accurate within 0.05 ppm.

<sup>1</sup>H NMR spectra were obtained using a Varian HA-100 resolution spectrometer working at 100 MHz.

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\* Value calculated using literature data on the molecular geometry<sup>19</sup> and on individual moments.<sup>4</sup>

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