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# The three-dimensional structure of 3, 3′, 5′-trichloro-4-methoxybiphenyl, a "coplanar" polychlorinated biphenyl (PCB) derivative

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**Abstract**

The crystal structure of a "coplanar" polychlorinated biphenyl (PCB) derivative, 4-methoxy-3, 3′, 5′-trichlorobiphenyl ($C_{13}H_9Cl_3O$), is described. The torsion angle of the title compound is 41.31(07)°, which is in good agreement with the calculated torsion angle of 38.2° in aqueous solution. 

*Keywords:* Environmental contaminants; Biaryls; PCB; Crystal structure

## 1. Introduction

Polychlorinated biphenyls (PCBs) are persistent environmental contaminants (Hansen, 1999). Due to their lipophilic character and resistance to degradation, PCBs tend to accumulate in the food chain, where they represent an environmental and human health hazard (Robertson and Hansen, 2001). PCBs are metabolized in vivo to hydroxy- and sulfur-containing metabolites. Hydroxylation proceeds primarily at the meta and para positions either via an arene oxide or by direct insertion of a hydroxyl group (Letcher et al., 2000). Several monohydroxy metabolites of higher chlorinated biphenyls have been found in human serum (Bergman et al., 1994), and are therefore relevant to human health. Recent evidence has been presented that PCBs and their metabolites may bind to a number of endogenous receptors, for example, the aryl hydrocarbon, ryanodine, constitutive androstane, estrogen receptors and others. Knowledge of structural detail, for example the three-dimensional structure of PCBs, will aid in our understanding of these interactions (Robertson and Hansen, 2001). Future studies will show how the three-dimensional structure of PCBs and their metabolites determine their biological and toxic effects (Andersson et al., 1999).

Few crystal structures of PCB metabolites have been published. The three-dimensional structure of PCBs is strongly associated with the torsion angle between the two phenyl rings. A comparison of the literature data shows that the torsion angle depends on the degree of chlorination in the ortho positions. According to published data, mono-ortho, di-ortho and tetra-ortho substituted PCBs show dihedral angles of 49–58°, 58–67° and 86–87°, respectively (summarized by Miao et al., 1997; see also: Singh et al., 1986; Mannila and Rissanen, 1994; Lehmler et al., 2001). The dihedral angles of two methoxylated PCBs, 2, 2′, 3, 4′, 5′-pentachloro-4-methoxybiphenyl and 2, 2′, 4, 4′, 5′, 6-hexachloro-3-methoxybiphenyl, were found to be 75.35(9)° and 82.7(1)°, respectively (summarized by Mannila et al., 1994).

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Here we report the crystal structure of a methoxylated PCB, 3, 3′, 5′-trichloro-4-methoxy biphenyl, which is structurally related to PCB metabolites found in human samples. Fig. 1 shows a thermal ellipsoid plot and Fig. 2 the molecular packing of the title compound. As shown in Scheme 1, the title compound has some structural resemblance to 3, 3′, 5, 5′-tetrachloro-4, 4′-dihydroxybiphenyl and 3, 3′, 4, 4′-tetrachlorobiphenyl. The mechanism of toxicity of PCBs without ortho chlorine substituents is similar to that of dioxins. PCB derivatives and metabolites without ortho chlorine atoms may show dioxin-like toxicity or alternatively may exert their toxicity via interaction with other cellular targets, for example the estrogen receptor.

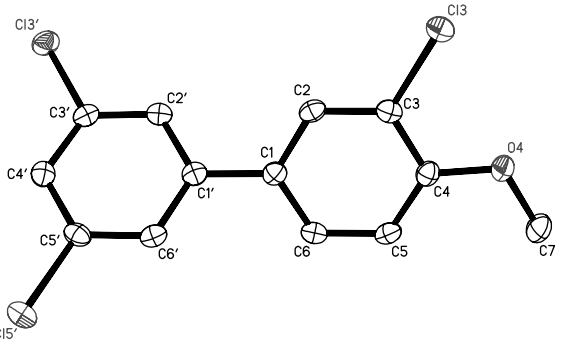



Fig. 1. Molecular structure of 3, 3′, 5′-trichloro-4-methoxybiphenyl.

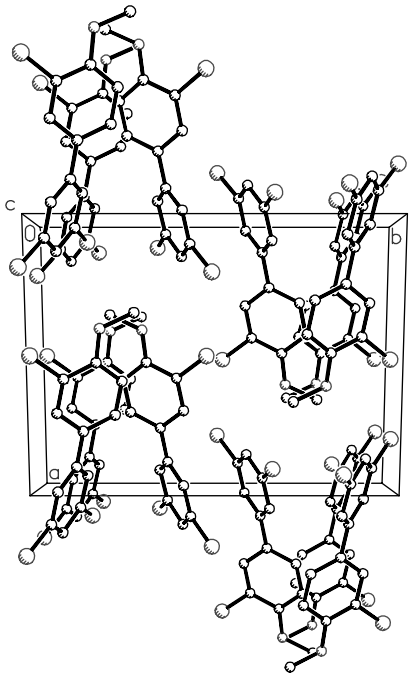
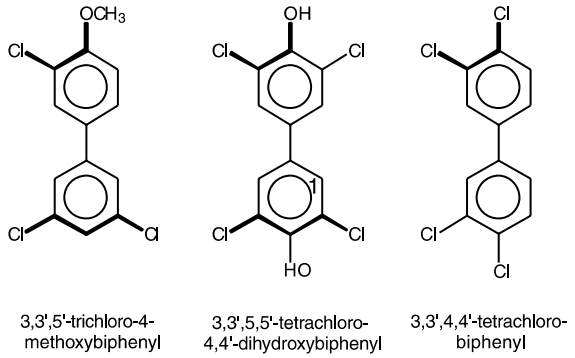



Fig. 2. Packing of 3, 3′, 5′-trichloro-4-methoxybiphenyl molecules.




Scheme 1. Structure of 3, 3′, 5′-trichloro-4-methoxy-, 3, 3′, 5, 5′-tetrachloro-4, 4′-dihydroxy- and 3, 3′, 4, 4′-tetrachlorobiphenyl.

The title compound shows a solid state torsion angle of 41.31(07)°, which, as expected, is smaller than the torsion angle of any ortho substituted PCB derivative. The torsion angle in aqueous solution was calculated to be 38.2° (see Section 2 for details of the calculation), which is very close to the value observed in the solid state. However, the structurally similar 3, 3′, 5, 5′-tetrachloro-4, 4′-dihydroxybiphenyl is perfectly coplanar in the solid state whereas the torsion angle in solution of 38.2° is identical to the value calculated for 3, 3′, 5′-trichloro-4-methoxy biphenyl (Fig. 3). These data indicate that packing effects may affect the torsion angle between the two phenyl rings of PCBs in the solid state. It is well known that, compared to the gas phase, *ortho* unsubstituted biphenyls adopt a flatter, but high-energy conformation in the solid state. Such a conformation allows a more dense

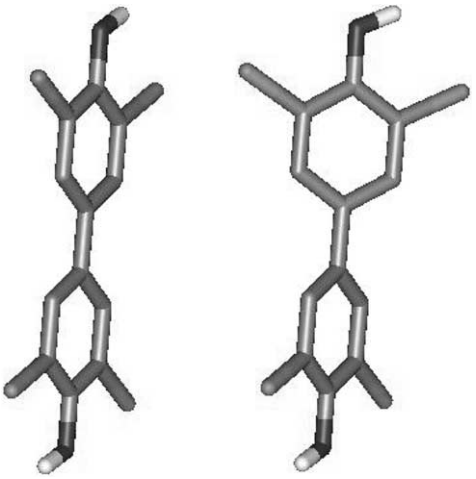


Fig. 3. Molecular structure of 3, 3′, 5, 5′-tetrachloro-4, 4′-dihydroxybiphenyl in the solid state (left) and aqueous solution (right). See experimental part for details on the calculation of the structure in aqueous solution.

packing of the biphenyl molecules in the crystal (Brock and Minton, 1989). The solid state torsion angle is therefore less meaningful for the prediction of biological activity, i.e., receptor binding.

## 2. Experimental

3,3′,5′-Trichloro-4-methoxybiphenyl was synthesized in 78% yield by the palladium-catalyzed cross coupling of 3,5-dichlorobenzene boronic acid and 4-bromo-2-chloroanisole (Lehmler and Robertson, 2001a,b). Colorless crystals were obtained upon crystallization from *n*-hexanes/ethylacetate; m.p. = 142–143 °C. $^1$H-NMR ($CDCl_3$, 200 MHz) $\delta$ 3.92 (s, $OCH_3$, 3H), 6.96 (d, $J_{ortho} = 8.4$ Hz, H-5), 7.28 (t, $J_{meta} = 2.0$ Hz, H-4′), 7.36 (d, $J_{ortho} = 8.4$ Hz, d, $J_{meta} = 2.2$ Hz, H-6), 7.36 (d, $J_{meta} = 2.0$ Hz, H-2′,6′), 7.53 (d, $J_{meta} = 2.2$ Hz, H-2′*). $^{13}$C-NMR ($CDCl_3$, 50 MHz) $\delta$ 56.25 ($OCH_3$), 112.41, 123.28, 125.20 (2 × C), 126.35, 127.11, 128.84, 131.88, 135.45 (2 × C), 142.57, 155.41. MS *m*/*z* (relative intensity, %): 286 (100, $C_{13}H_9Cl_3O^{\cdot+}$), 271 (51, M–$CH_3$), 243 (39, M–CO–$CH_3$), 173 (39, M–CO–$CH_3$–$Cl_2$). IR [$cm^{-1}$]: 3070, 3019, 2977, 2936, 2841, 1552, 1431, 1297, 1266, 1062, 1018, 860, 796, 702. Elemental Analysis Calcd. for $C_{13}H_9Cl_3O$: C 54.30, H 3.15; found: C 54.41, H 3.17.

X-ray diffraction data were collected at 173 K on a Nonius kappaCCD diffractometer from an irregular block-shaped crystal. Raw data were integrated, scaled, merged and corrected for Lorentz-polarization effects using the HKL-SMN package (Otwinowski and Minor, 1997). The structure was solved by direct methods (Sheldrick, 1997) and difference Fourier (Sheldrick, 1997). Refinement was carried out against $F^2$ by weighted full-matrix least-squares (Sheldrick, 1997). Hydrogen atoms were found in difference maps but subsequently placed at calculated positions and refined using a riding model. Non-hydrogen atoms were refined with anisotropic displacement parameters. Atomic scattering factors were taken from the International Tables for Crystallography (Prince, 1992). Crystal data and relevant details of the structure determinations are summarized in Table 1. Bond lengths and angles are given in Table 2. Further details of the crystal structure analysis are available from the Cambridge Structural Database.

The dihedral angles of 3,3′,5′-trichloro-4-methoxybiphenyl and 3,3′,5,5′-tetrachloro-4,4′-dihydroxybiphenyl were calculated with MM2* using GB/SA water solvent continuum as implemented by MacroModel 5.0 (Still et al., 1990).

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Table 1
Crystal data and structure refinement for 3,3′,5′-trichloro-4-methoxybiphenyl

| | |
|---|---|
| Empirical formula | $C_{13}H_9Cl_3O$ |
| Formula weight | 287.55 |
| Temperature | 173(1) K |
| Wavelength | 0.71073 Å |
| Crystal system, space group | Monoclinic, P $2_1/c$ |
| Unit cell dimensions | $a = 11.277(2)$ Å, alpha = 90° |
| | $b = 14.390(3)$ Å, beta = 107.41(3)° |
| | $c = 7.8910(16)$ Å, gamma = 90° |
| Volume | 1221.9(4) Å$^3$ |
| Z, Calculated density | 4, 1.563 Mg/m$^3$ |
| Absorption coefficient | 0.727 mm$^{-1}$ |
| *F*(000) | 584 |
| Crystal size | 0.38 × 0.28 × 0.18 mm |
| Theta range for data collection | 1.89 to 27.46 deg. |
| Limiting indices | $-14 \leqslant h \leqslant 14$, $8 \leqslant k \leqslant 18$, $10 \leqslant l \leqslant 10$ |
| Reflections collected/unique | 5466/2799 [*R*(int) = 0.0201] |
| Completeness to theta = 27.46 | 99.9% |
| Absorption correction | Empirical (XABS2) (Parkin et al., 1995) |
| Max. and min. transmission | 0.8802 and 0.7696 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data/restraints/parameters | 2799/0/156 |
| Goodness-of-fit on $F^2$ | 1.053 |
| Final *R* indices [$I > 2$sigma($I$)] | $R1 = 0.0270$, $wR2 = 0.0661$ |
| *R* indices (all data) | $R1 = 0.0343$, $wR2 = 0.0694$ |
| Extinction coefficient | 0.0154(11) |
| Largest diff. peak and hole | 0.304 and −0.215 eÅ$^{-3}$ |

Table 2
Bond lengths [Å] and angles [°] for 3, 3′, 5′-trichloro-4-methoxybiphenyl

| | | | |
|---|---|---|---|
| C(1)–C(6) | 1.393(2) | C(1)–C(2) | 1.398(2) |
| C(1)–C(1′) | 1.487(2) | C(2)–C(3) | 1.383(2) |
| C(3)–C(4) | 1.398(2) | C(3)–Cl(3) | 1.7398(15) |
| C(4)–O(4) | 1.3612(17) | C(4)–C(5) | 1.391(2) |
| C(5)–C(6) | 1.386(2) | O(4)–C(7) | 1.4352(18) |
| C(1′)–C(6′) | 1.395(2) | C(1′)–C(2′) | 1.399(2) |
| C(2′)–C(3′) | 1.383(2) | C(3′)–C(4′) | 1.384(2) |
| C(3′)–Cl(3′) | 1.7444(15) | C(4′)–C(5′) | 1.383(2) |
| C(5′)–C(6′) | 1.382(2) | C(5′)–Cl(5′) | 1.7430(15) |
| C(6)–C(1)–C(2) | 118.38(13) | C(6)–C(1)–C(1′) | 121.05(13) |
| C(2)–C(1)–C(1′) | 120.57(13) | C(3)–C(2)–C(1) | 120.09(13) |
| C(2)–C(3)–C(4) | 121.46(13) | C(2)–C(3)–Cl(3) | 119.77(11) |
| C(4)–C(3)–Cl(3) | 118.76(11) | O(4)–C(4)–C(5) | 125.03(14) |
| O(4)–C(4)–C(3) | 116.61(13) | C(5)–C(4)–C(3) | 118.36(13) |
| C(6)–C(5)–C(4) | 120.26(14) | C(5)–C(6)–C(1) | 121.44(14) |
| C(4)–O(4)–C(7) | 116.58(12) | C(6′)–C(1′)–C(2′) | 119.22(13) |
| C(6′)–C(1′)–C(1) | 120.06(13) | C(2′)–C(1′)–C(1) | 120.69(13) |
| C(3′)–C(2′)–C(1′) | 119.15(13) | C(2′)–C(3′)–C(4′) | 122.67(13) |
| C(2′)–C(3′)–Cl(3′) | 119.02(11) | C(4′)–C(3′)–Cl(3′) | 118.30(11) |
| C(5′)–C(4′)–C(3′) | 117.01(13) | C(6′)–C(5′)–C(4′) | 122.44(13) |
| C(6′)–C(5′)–Cl(5′) | 118.77(11) | C(4′)–C(5′)–Cl(5′) | 118.74(11) |
| C(5′)–C(6′)–C(1′) | 119.50(13) | | |

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