

Crystal and Energy-Refined Structures of 4,4'-Dichloro-3,3',5,5'-tetrafluorobiphenyl

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Abstract. $C_{12}H_4Cl_2F_4$, $M_r = 295.07$, monoclinic, $P2_1/c$, $a = 11.898$ (2), $b = 13.013$ (2), $c = 7.256$ (1) Å, $\beta = 99.32$ (1)°, $V = 1108.61$ Å³, $Z = 4$, $D_x = 1.768$ Mg m⁻³, $\lambda(\text{Cu } K\alpha) = 1.54178$ Å, $\mu = 5.73$ mm⁻¹, $F(000) = 584$, $T = 293$ K, $R = 0.051$ for 941 observed reflections, $S = 2.8$. The dihedral angle between the two planar benzene rings is 33.7°. The crystal structure is compared with the energy-minimized molecular structure using molecular mechanics, giving results (34.5°) in excellent agreement. The results are discussed for their possible use and importance in assessing the availability of the coplanar conformation in *ortho*-unsubstituted biphenyl for determining their receptor binding potency and toxicity in biological systems.

Introduction. Polychlorinated biphenyls (PCB's) were commercially produced in several countries as complex mixtures for a variety of uses, including dielectric fluids in capacitors and transformers. Since PCB's do not readily degrade in the environment after disposal or dissemination and are lipophilic, they are persistent and tend to bioaccumulate (Jensen, Johnels, Olsson & Olterlind, 1969). Their toxicities in laboratory animals have been shown to be remarkably dependent on both the number and positions of chlorine substituents. Identification and characterization of specific PCB structures found in biological samples may be important not only for assessment of long-term persistence but also for evaluation of potential health effects (McKinney, Chae, McConnell & Birnbaum, 1985). One of the most toxic PCB's known is the 3,3',-4,4',5,5'-hexachlorobiphenyl congener for which it has not been possible to determine a complete crystal structure. The title compound, a close structural relative of this toxic PCB, was prepared and its toxicity tested (McKinney, Singh, Levy & Walker, 1980) as one of several molecular probes for examining the structure-activity relationships of PCB's. X-ray crystallography and computational chemistry (energy calculations)

have been shown to be complementary techniques for investigating the various possible conformations (and their relative energies) of a given PCB molecule (Singh, Pedersen & McKinney, 1986). In this work we compare the crystal and energy-refined (from molecular mechanics, *MM2p*) structures of 4,4'-dichloro-3,3',-5,5'-tetrafluorobiphenyl.

Experimental. Compound synthesis and crystallization reported previously (McKinney, Singh, Levy & Walker, 1980). Plate-like crystals of approximate dimensions 0.20 × 0.15 × 0.05 mm, space group determined by means of Weissenberg and precession photographs. Crystals slightly unstable; intensity data collected from an epoxy-coated crystal with Cu $K\alpha$ radiation on a Nicolet P3/F diffractometer equipped with a graphite monochromator and a pulse-height analyzer. Lattice parameters from 15 high-angle reflections. Intensities collected by the $\theta/2\theta$ scan technique in the range $2 \leq 2\theta \leq 100^\circ$, $h -11$ to $+11$, $k 0$ to 12 , $l 0$ to 7 ; 1280 unique reflections measured, 941 with $I \geq 2\sigma(I)$ used in structure determination. One reflection (012) used as a standard, $\pm 2\%$ fluctuation in intensity. Empirical absorption correction *via* ψ -scan applied (max. and min. transmission factors 0.45, 0.71). No extinction corrections made; two low-angle strong reflections (200 and 012) showed extinction error and were removed from the data set. Structure solved using *MULTAN78* (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) which revealed all but the H atoms; H atoms located from a difference Fourier synthesis. Non-H-atom coordinates refined with anisotropic temperature factors, H atoms with a fixed isotropic temperature factor of 3.0 Å². Anomalous dispersion of Cl for Cu $K\alpha$ was used. Full-matrix least-squares refinement carried out on F , the function minimized being $\sum w(|F_o| - |F_c|)^2$, where $w = 4F_o/\sigma^2(I)$; $\sigma^2(I)$ from counting statistics, including an additional term $(0.02I)^2$. $R = 0.051$, $wR = 0.055$ for 941 observations and 179 refined parameters. The maximum shift/e.s.d. in the final cycle was 0.1 for non-H and 0.2 for H atoms. Final $\Delta\rho$ fluctuation in the difference map < 0.5 e Å⁻³. Atomic scattering factors and anomalous-dispersion corrections from *International Tables for X-ray Crystallography* (1974).

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Molecular mechanics was carried out by a Fortran version prepared for *PROPHET* based upon the *MM2* program of Allinger & Yuh (1981), as modified by D. Rohrer for inclusion of π atoms (Duax, Franckoviak, Griffin & Rohrer, 1982) and more recently by D. Barry at Bolt Beranek & Newman Inc. (contractors for *PROPHET*), to include the out-of-plane bending due to a halide at a C_{sp^2} alkene atom (*MM2p*, version 2.5). The standard out-of-plane bending parameters for the function ($\theta = 0^\circ$; $k_s = 0.5 \text{ nN \AA}^{-1}$) were included by the system along with the standard 1982 force field. The following nonstandard parameters were entered: (1: sp^3 -carbon; 2: aromatic sp^2 -carbon; 5: hydrogen; 12: chloride; and 11: fluoride): bonds l_0 (\AA): 2-12 = 1.697 (this report), 2-11 = 1.36 (this report) and k_s (nN \AA^{-1}): 2-12 = 26.6 (Yamamoto & Oki, 1985) and 2-11 = 44 (Meyer, 1980); angles θ ($^\circ$): 2-2-12 = 2-2-11 = 120 and k_b (nN \AA rad^{-2}): 2-2-12 = 5.6 (deduced from standard tables) and 2-2-11 = 6.5 (deduced from standard tables); dihedrals V_1, V_2, V_3 (kJ mol^{-1}): 12-2-2-11 = 2-2-2-11 = 12-2-2-2 = 5-2-2-11 = 4.2, 62.7, 4.2 (deduced from standard tables and Yamamoto & Oki, 1985). Slightly higher minimized energies occurred when the following simultaneous changes were made: $l_0 = 1.710$ for Cl and 1.34 for F; $k_b = 10$ for both 2-2-12 and 2-2-11; $k_s = 30$ for 2-12 and 50 for 2-11. Although a 0.04% lower minimized energy was obtained with $k_b = 4$ for 2-2-12 and 6 for 2-2-11, the parameters stated above were used. No further attempt was made to optimize the parameters fully.

The molecule was drawn on the tablet and the COMPUTE MODEL command assigned initial atomic coordinates, in this case by comparison with a standard benzene ring (Rindone & Kush, 1980). The molecule was then given twists of from 0 to 180° at the C(1)-C(1') bond. The *MM2 MODEL* program initially performs a VESCF (variable-electron self-consistent field) quantum-mechanical π -system calculation to adjust the force-field parameters. An initial steric energy is then computed after this adjustment; it is these energies that are shown on the curve of Fig. 3. The program then carries out repeated combinations of a VESCF and iterative SCF calculations to optimize the geometry and reach overall consistency (Allinger & Graham, 1973; Allinger & Sprague, 1973).

Discussion. The fractional coordinates derived from the last cycle of refinement are presented in Table 1.* An *ORTEP* (Johnson, 1976) view of the molecule looking

* Lists of bond distances and angles associated with non-H atoms, anisotropic thermal parameters and observed and calculated structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43295 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

down the normal to the benzene ring containing atoms C(1) through C(6) along with the atom-numbering system is shown in Fig. 1. A stereopacking diagram is shown in Fig. 2.

Table 1. Fractional atomic coordinates for the title compound (*e.s.d.*'s in parentheses)

$$U_{eq} = (U_{11}U_{22}U_{33})^{1/3}.$$

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{eq}(\text{\AA}^2)$
Cl(4)	0.6816 (1)	0.0429 (1)	0.2877 (3)	0.077
Cl(4')	-0.1336 (2)	0.3133 (1)	0.4153 (3)	0.082
F(3)	0.4665 (3)	-0.0627 (3)	0.1537 (5)	0.071
F(5)	0.6215 (3)	0.2255 (3)	0.4833 (6)	0.080
F(3')	-0.0644 (3)	0.0987 (3)	0.4156 (5)	0.075
F(5')	0.0698 (3)	0.4329 (3)	0.3754 (6)	0.075
C(1)	0.3280 (5)	0.1515 (5)	0.3434 (8)	0.042
C(2)	0.3443 (5)	0.0586 (5)	0.2518 (8)	0.048
C(3)	0.4528 (6)	0.0279 (5)	0.2422 (8)	0.051
C(4)	0.5483 (5)	0.0814 (5)	0.3119 (8)	0.050
C(5)	0.5294 (5)	0.1715 (5)	0.4029 (9)	0.054
C(6)	0.4233 (6)	0.2056 (5)	0.4209 (9)	0.052
C(1')	0.2136 (5)	0.1889 (5)	0.3587 (7)	0.041
C(2')	0.1249 (5)	0.1243 (5)	0.3754 (8)	0.047
C(3')	0.0222 (5)	0.1627 (5)	0.3940 (8)	0.051
C(4')	-0.0029 (5)	0.2677 (5)	0.3937 (8)	0.051
C(5')	0.0882 (6)	0.3291 (5)	0.3727 (8)	0.053
C(6')	0.1930 (5)	0.2953 (5)	0.3561 (8)	0.049
H(2)	0.284 (5)	0.021 (5)	0.202 (8)	0.038
H(6)	0.420 (5)	0.259 (5)	0.489 (9)	0.038
H(2')	0.133 (5)	0.049 (5)	0.376 (8)	0.038
H(6')	0.253 (5)	0.335 (5)	0.346 (8)	0.038

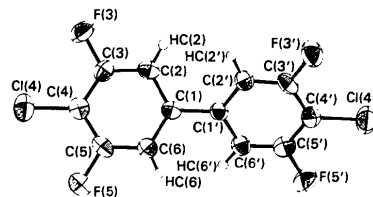


Fig. 1. *ORTEP* (Johnson, 1976) view of the title compound looking down the benzene ring containing atoms C(1) through C(6), along with the atom-numbering system.

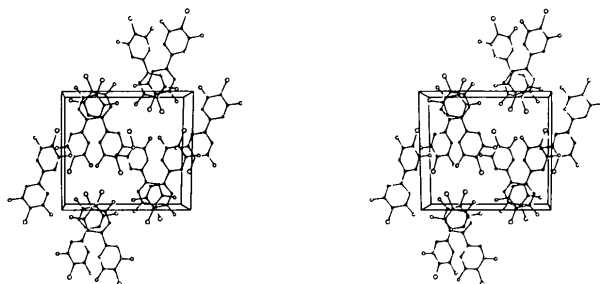


Fig. 2. Stereoview of the crystal packing down the *c* axis. Origin is in the lower right-hand corner with the *a* axis vertical and the *b* axis horizontal.

The two C—Cl bond distances are considerably shortened [1.695 (6) and 1.699 (6) Å] owing to the strongly inductive neighboring *ortho* F atoms (Kaftory, 1983). Many of the ring bonds are also shortened considerably as is also found with other fluorinated biphenyls. The C(1)—C(1') bond is on the shorter side for biphenyls, 1.467 (8) Å.

The ring angles at the F atom (γ in biphenyl) are enlarged (124.9, 124.0, 123.2 and 125.4°) while the ring angles at the Cl atoms (δ in biphenyl) are considerably reduced (114.9 and 113.3°). The ring angles at the H atoms (β in biphenyl) were found from a large number of molecules to be an average of +1.0 (1)° (Domenicano & Murray-Rust, 1979) and +0.87 (8)° (Norrestam & Schepper, 1981) above 120° (e.s.d. given as units in the last digit). The average reduction of the four β biphenyl angles here was -0.4°, giving an angle of 119.6°, owing to a combination of the effects of the neighboring F atom and the reduced α biphenyl angles, as usually found, associated with torsion around the C(1)—C(1') bond (117.7 and 118.1° in this report).

Mean planes through the six C atoms of individual benzene rings show that none of the C atoms deviates by more than 0.01 Å from the plane. The dihedral angle between the planes is 33.7° which is 12.9° smaller than that found in another *ortho*-unsubstituted biphenyl, 3,3',4,4'-tetrabromobiphenyl, whose structure has been reported from this laboratory (McKinney & Singh, 1981) and smaller than for many other *ortho*-unsubstituted biphenyls. Since the highly inductive and electronegative F atoms (Domenicano, Mazzeo & Vaciago, 1976; Kaftory, 1983) greatly shorten their neighboring C—Cl bonds, they may similarly shorten their neighboring C—H bonds, possibly reducing steric interactions and permitting a flatter overall molecule. It may be pointed out that biphenyl itself and a number of *ortho*-unsubstituted biphenyls in

the crystalline state have inter-ring dihedral angles of zero or close to zero (McKinney & Singh, 1981, Table 1).

The single-cycle VESCF calculated curve of torsionally associated potentials, computed using constrained angles of torsion at the central bond, is symmetrical between 0 and 90° with that between 90 and 180°. The initial energy minimum is at 48° (Fig. 3). At 90° there is a local minimum corresponding to the perpendicularly stabilized conformer. The energy barrier at 90° is 3.34 kJ mol⁻¹ and it is 25.5 kJ mol⁻¹ at 0 and 180°. After iterative energy minimization by the *MM2p* program, the final minimum is at 34.5°. This structure is essentially identical to that obtained by X-ray analysis, 33.7°. The final steric energies are: 24.4 kJ mol⁻¹ at 34.5°, 30.3 kJ mol⁻¹ at 90°, and 32.2 kJ mol⁻¹ at 0 and 180°.

It is interesting to note that the title compound is relatively non-toxic (no signs of toxicity at six times the LD₅₀ dose of the toxic compound) compared with 3,3',4,4',5,5'-hexachlorobiphenyl, and this difference is not likely to be due to a difference in pharmacokinetic properties (McKinney, Chae, McConnell & Birnbaum, 1985). Since the toxic PCB would be expected also to have a wide range of thermally accessible dihedral angles including the coplanar state, it is unlikely that this difference is due to different conformational properties of the molecules. A theoretical model for a postulated receptor binding interaction involved in toxicity has recently been developed (McKinney, Darden, Lyerly & Pedersen, 1985). The essential parameters in the model are the PCB polarizability and the receptor-to-PCB separation distance. Since the receptor-to-PCB separation distance is likely to be the same (or nearly the same) for the toxic and relatively nontoxic title PCB, its predicted lower binding energy in the receptor binding model would be associated with the less polarizable C—F bonds and overall lower molecular polarizability.

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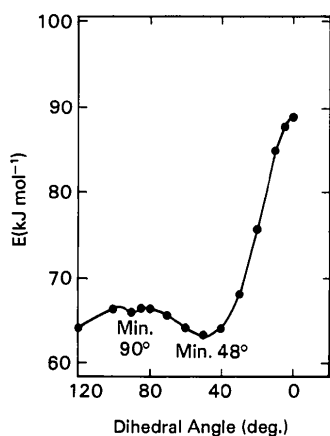


Fig. 3. Torsional potential curve. The torsion angle is the dihedral angle between the two ring planes.

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Structures of 9-Hydroxy-5,8-dimethoxy-1,4-phenanthrenequinone, (1), and 3,5,8-Trimethoxy-1,4-phenanthrenequinone, (2)

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Abstract. (1) $C_{16}H_{12}O_5$, $M_r = 284.27$, triclinic, $P\bar{1}$, $a = 7.221$ (1), $b = 10.071$ (19), $c = 10.474$ (1) Å, $\alpha = 64.46$ (1), $\beta = 68.97$ (1), $\gamma = 80.85$ (1)°, $V = 641.5$ (1) Å³, $Z = 2$, $D_x = 1.472$ Mg m⁻³, Cu $K\alpha$ radiation, $\lambda = 1.5418$ Å, $\mu = 0.823$ mm⁻¹, $F(000) = 296$, $T = 296$ K, final $R = 0.048$ for 1507 observed reflections. (2) $C_{17}H_{14}O_5$, $M_r = 298.30$, monoclinic, $P2_1/n$, $a = 8.442$ (1), $b = 25.129$ (1), $c = 6.717$ (1) Å, $\beta = 98.18$ (1)°, $V = 1410.4$ (2) Å³, $Z = 4$, $D_x = 1.405$ Mg m⁻³, Cu $K\alpha$ radiation, $\mu = 0.771$ mm⁻¹, $F(000) = 624$, $T = 296$ K, final $R = 0.052$ for 1861

observed reflections. The structures of (1) and (2) exhibit helical distorted molecules of optical antipodes which are located across centres of symmetry. The deviations of atoms O(4) and O(5) from the plane C(9) to C(12) are similar for both compounds: 1.108 (4) and -0.811 (4) Å for (1), and -1.075 (3) and 0.849 (3) Å for (2). The molecules in the crystal are held together by weak intermolecular C–H...O interactions and van der Waals forces.

Introduction. The naturally occurring phenanthrenequinone (PQ) cypripedin has been shown to possess a sensitizing capacity (Hausen, 1982). To obtain more information on relationships between chemical structure and allergenic properties of PQs, some 30 mono-,

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