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Crystal and Energy-Refined Structures of 2,2′,4,4′,5,5′-Hexachlorobiphenyl*

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Abstract. $C_{12}H_4Cl_6$, $M_r = 360{\cdot}82$, monoclinic, $P2_1/n$, $a = 12{\cdot}395$ (2), $b = 8{\cdot}044$ (1), $c = 13{\cdot}388$ (2) Å, $\beta = 94{\cdot}45$ (1)°, $V = 1330{\cdot}83$ Å^3, $Z = 4$, $D_x = 1{\cdot}80$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 12{\cdot}7$ cm^{-1}, $F(000) = 712$, $T = 293$ K, $R = 0{\cdot}024$ for 1075 observed reflections. The bond distances and bond angles in the title compound are similar to those found in other halogenated biphenyls. The two benzene rings are planar; however, the two rings are not coplanar. Taking the *trans*-coplanar arrangement of Cl(2) and Cl(2′) as 0°, the dihedral angle between the rings is 58·3°. The crystal structure is compared with the energy-minimized molecular structures using the *ab initio* quantum-mechanical and molecular-mechanics methods, giving results in substantial agreement. The results are discussed for their possible use and importance in assessing the polychlorinated biphenyl *ortho* effect which appears to be important in determining receptor binding potency and toxicity of these compounds in biological systems.

Introduction. Polychlorinated biphenyls (PCB's) are a well known class of chemicals which have been industrially produced in several countries for many years. The complexity of PCB mixtures introduced into the environment results in the presence of many individual PCB congeners in human tissues. Jensen & Sundstrom (1974) determined 40 PCB congeners in human tissue. One compound, 2,2′,4,4′,5,5′-hexachlorobiphenyl, accounted for 22% of the PCB's in tissue. Thus, this PCB may be the single most important (from a concentration point of view) congener found in human tissue and is representive of the many *ortho*-substituted PCB's which constitute the PCB residue in humans. Identification and characterization of specific PCB structures in human tissues may be important not only for assessment of long-term persistence but also for evaluation of potential health effects (McKinney, Chae, McConnell & Birnbaum, 1985).

X-ray crystallographic determinations can provide a highly accurate picture of molecular geometry in a specific solid-state environment. For most uncharged molecules like the title compound, a structure observed in the solid state is at or very near a local minimum-energy conformation. Because the active forms of toxic compounds may not necessarily be low-energy forms, it is important to have reliable information on the various conformations and their relative energies of a given molecule that may not be readily crystallizable. In this work, we compare the crystal and energy-refined structures of 2,2′,4,4′,5,5′-hexachlorobiphenyl.

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* The following paper reports an independent structure determination of this compound.

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Experimental. Compound synthesis has been previously reported (McKinney, Chae, Gupta, Moore & Goldstein, 1976). Crystallization from benzene solution, colorless plate-like crystals of irregular shape, approximate dimensions 0·25 × 0·15 × 0·10 mm, space group determined by means of Weissenberg and precession photographs. Intensity data collected on Syntex *P*1 diffractometer, Zr-filtered Mo $K\alpha$. Lattice parameters from 15 reflections. Intensities collected in range $0 < 2\theta < 42°$, *h* −12 to +12, *k* 0 to 8, *l* 0 to 13; 1537 reflections measured, 1075 with $I \geq 2\sigma(I)$ used in structure determination. One standard reflection, ±1·5% fluctuation in intensity. No absorption correction made. Structure solved using *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) which revealed all non-H atoms; H atoms located from difference Fourier map. All atoms except H refined with anisotropic temperature factors; H-atom coordinates refined with a fixed isotropic temperature factor *B* of 4·0 Å^2. Anomalous dispersion of Cl for Mo $K\alpha$ used. Full-matrix least-squares refinement carried out on *F*, function minimized $\sum w(|F_o| - |F_c|)^2$, $w = 4F_o^2/\sigma^2(I)$, $R = 0·024$, $wR = 0·046$ for 1075 observations and 175 refined parameters. In final cycle max. shift/e.s.d. 0·02 for non-H and 0·04 for H atoms. Final $\Delta\rho$ fluctuation in difference map <0·2 e Å^{-3}. Atomic scattering factors and anomalous-dispersion corrections from *International Tables for X-ray Crystallography* (1974).

The molecular-mechanics (*MM*) program *MODEL* 1·3 kindly provided for the University of North Carolina by W. Clark Still (Columbia University) was used to perform approximate force-field calculations. This program was modified in our laboratory to utilize a Tektronix 4107 color-display terminal with graphics tablet input. *MODEL* 1·3 utilizes the *MM*2 force field (Burkert & Allinger, 1982); this force field does not include quantum-mechanical corrections. Cl parameters were estimated from Meyer, Allinger & Yuh (1980).

The *GAUSSIAN*82 *ab initio* quantum-mechanical (*QM*) basis set chosen was the built-in STO-3G basic (Binkley, Frisch, DeFrees, Raghavachari, Whiteside, Schelgel, Fluder & Pople, 1983); this basis leads to 118 orbitals and approximately 10^7 integrals for the various nuclear configurations. The average X-ray internal coordinates shown in Table 1 were adapted for the *ab initio* calculations. The molecular-mechanics parameters were fixed so that all C—C distances in the rings were maintained very close to 1·4 Å [bond constant = 9·6 mdyn Å^{-1} (1 dyn ≡ 10^{-5} N)], the C—Cl distance was chosen to be 1·745 Å with a force constant of 5·0 mdyn Å^{-1}, the C—C—Cl angle was chosen to be 120·0° with a force constant of 1·0 mdyn Å rad^{-2} and the out-of-plane C—C—C—Cl rotational barrier was chosen to be large (418·7 kJ mol^{-1}) so as to force the Cl into the ring plane. The central C—C bond was fixed at 1·50 Å with a force constant of 5·0 mdyn Å^{-1}. In both the *ab initio* and molecular-mechanics calculations single point energies were computed for rotation about the central C—C bond; for the *ab initio* rotation all atoms were rigidly fixed for all variables except for the rotation dihedral angle, whereas the molecular-mechanics procedure allowed relaxation within the entire molecule for the initial minimization.

Table 1. *Fractional atomic coordinates and isotropic thermal parameters for* 2,2′,4,4′,5,5′-*hexachlorobiphenyl*

E.s.d.'s given in parentheses pertain to the last decimal place.
$U_{eq} = (U_{11}U_{22}U_{33})^{1/3}$.

	x	*y*	*z*	U_{eq}/U_{iso}(Å^2)
Cl(2)	−0·6731 (1)	0·0385 (2)	0·3137 (1)	0·0512
Cl(4)	−0·5397 (1)	0·2898 (2)	0·6709 (1)	0·0529
Cl(5)	−0·3254 (1)	0·4184 (2)	0·5842 (1)	0·0502
Cl(2′)	−0·2767 (1)	0·0293 (2)	0·2782 (1)	0·0444
Cl(4′)	−0·4141 (1)	0·1970 (2)	−0·0943 (1)	0·0539
Cl(5′)	−0·6246 (1)	0·3576 (2)	−0·0172 (1)	0·0562
C(1)	−0·4830 (4)	0·2087 (6)	0·3453 (3)	0·0324
C(2)	−0·5754 (4)	0·1477 (6)	0·3863 (3)	0·0351
C(3)	−0·5910 (4)	0·1705 (7)	0·4868 (4)	0·0379
C(4)	−0·5161 (4)	0·2549 (6)	0·5473 (3)	0·0363
C(5)	−0·4224 (4)	0·3139 (6)	0·5095 (3)	0·0363
C(6)	−0·4073 (4)	0·2899 (6)	0·4091 (4)	0·0345
C(1′)	−0·4663 (4)	0·1980 (6)	0·2362 (3)	0·0320
C(2′)	−0·3752 (4)	0·1267 (6)	0·1995 (3)	0·0338
C(3′)	−0·3596 (4)	0·1269 (7)	0·0991 (4)	0·0397
C(4′)	−0·4361 (4)	0·1977 (6)	0·0318 (4)	0·0372
C(5′)	−0·5275 (4)	0·2694 (6)	0·0657 (4)	0·0365
C(6′)	−0·5410 (4)	0·2693 (7)	0·1671 (4)	0·0384
HC(3)	−0·652 (4)	0·130 (6)	0·509 (3)	0·0380
HC(6)	−0·347 (4)	0·334 (6)	0·386 (3)	0·0380
HC(3′)	−0·302 (4)	0·079 (6)	0·077 (3)	0·0380
HC(6′)	−0·598 (4)	0·316 (6)	0·188 (3)	0·0380

Table 2. *Bond distances* (Å) *and bond angles* (°) *in* 2,2′,4,4′,5,5′-*hexachlorobiphenyl not including* H *atoms*

Numbers in parentheses are e.s.d.'s in the last decimal place.

C(1)—C(1′)	1·493 (7)	C(1′)—C(2′)	1·390 (6)
C(1)—C(2)	1·398 (6)	C(1′)—C(6′)	1·381 (7)
C(1)—C(6)	1·383 (7)	C(2′)—C(3′)	1·373 (6)
C(2)—C(3)	1·385 (7)	C(2′)—Cl(2′)	1·736 (5)
C(2)—Cl(2)	1·732 (5)	C(3′)—C(4′)	1·379 (7)
C(3)—C(4)	1·365 (7)	C(4′)—C(5′)	1·379 (7)
C(4)—C(5)	1·386 (6)	C(4′)—Cl(4′)	1·730 (5)
C(4)—Cl(4)	1·726 (5)	C(5′)—C(6′)	1·381 (7)
C(5)—C(6)	1·385 (7)	C(5′)—Cl(5′)	1·725 (5)
C(5)—Cl(5)	1·723 (5)		

C(1′)—C(1)—C(2)	123·0 (4)	C(1)—C(1′)—C(2′)	123·2 (4)
C(1′)—C(1)—C(6)	119·5 (4)	C(1)—C(1′)—C(6′)	119·7 (4)
C(2)—C(1)—C(6)	117·4 (4)	C(2′)—C(1′)—C(6′)	117·1 (4)
C(1)—C(2)—C(3)	121·0 (5)	C(1′)—C(2′)—C(3′)	121·7 (5)
C(1)—C(2)—Cl(2)	121·0 (4)	C(1′)—C(2′)—Cl(2′)	121·6 (3)
C(3)—C(2)—Cl(2)	118·0 (4)	C(3′)—C(2′)—Cl(2′)	116·7 (4)
C(2)—C(3)—C(4)	120·2 (5)	C(2′)—C(3′)—C(4′)	119·9 (5)
C(3)—C(4)—C(5)	120·2 (4)	C(3′)—C(4′)—C(5′)	119·8 (4)
C(3)—C(4)—Cl(4)	119·5 (4)	C(3′)—C(4′)—Cl(4′)	118·9 (4)
C(5)—C(4)—Cl(4)	120·3 (4)	C(5′)—C(4′)—Cl(4′)	121·2 (4)
C(4)—C(5)—C(6)	119·2 (5)	C(4′)—C(5′)—C(6′)	119·3 (5)
C(4)—C(5)—Cl(5)	121·4 (4)	C(4′)—C(5′)—Cl(5′)	120·7 (4)
C(6)—C(5)—Cl(5)	119·4 (4)	C(6′)—C(5′)—Cl(5′)	120·1 (4)
C(5)—C(6)—C(1)	121·9 (4)	C(5′)—C(6′)—C(1′)	122·2 (5)

Discussion. *X-ray refinement.* The fractional coordinates derived from the last cycle of refinement are presented in Table 1. The bond distances and bond angles associated with the non-H atoms are shown in Table 2.* An *ORTEP*II (Johnson, 1976) view of the molecule looking 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.

The bond distances and bond angles in the title compound are similar to those found in other halogenated biphenyls. Thus, the C(1)—C(1′) distance of 1·493 (7) Å is within 2·0σ of that found for 2,2′,4,4′,6,6′-hexachlorobiphenyl [1·477 (8) Å] (Singh & McKinney, 1979), and is only 1·1σ away from the theoretically calculated value, 1·485 Å, between two sp^2-hybridized C atoms (Dewar & Schmeising, 1968). The mean of the twelve C—C bond distances in the two benzene rings is 1·382 Å which is normal. The six C—Cl bond distances range from 1·723 to 1·736 Å with a mean of 1·729 Å, which compares well with the mean C—Cl distance of 1·730 Å reported for the 2,2′,4,4′,6,6′-hexachloro isomer (Singh & McKinney, 1979). The ring bond angles at C(1) and C(1′), 117·4 and 117·1°, respectively, are similar to those observed for biphenyl and its derivatives (Singh & McKinney, 1979). The two exocyclic bond angles at C(1) and at C(1′) have significantly different values, C(1′)—C(1)—C(2) (123·0°) being larger than C(1′)—C(1)—C(6) (119·5°), and C(1)—C(1′)—C(2′) (123·2°) being larger than C(1)—C(1′)—C(6′) (119·7°). Similar values have been observed for 2,2′-dichlorobiphenyl (Rømming, Seip & Aanesen Øymo, 1974).

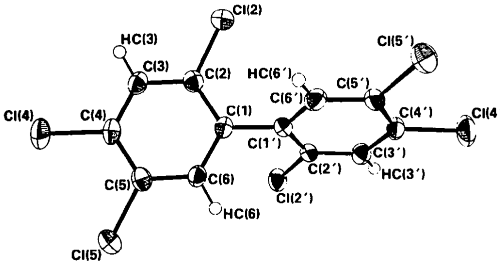

Fig. 1. *ORTEP*II (Johnson, 1976) view of the 2,2′,4,4′,5,5′-hexachlorobiphenyl molecule looking down the normal to the benzene ring containing atoms C(1) through C(6), along with the atom-numbering system.

Least-squares planes through the two benzene rings show them to be planar.* The two rings are, however, not coplanar, the dihedral angle between them being 58·3°. This value is less than when all four *ortho* positions are substituted by Cl atoms *e.g.* 87·3° for 2,2′,4,4′,6,6′-hexachlorobiphenyl (Singh & McKinney, 1979) and 86·6° for decachlorobiphenyl (Pedersen, 1975). It is somewhat similar to the value, 66·8°, found for 2,2′-dichlorobiphenyl in the solid state and between 70 and 75° found in the gaseous state (Rømming, Seip & Aanesen Øymo, 1974). The conformations of the title compound and 2,2′-dichlorobiphenyl, however, are quite different. For the title compound the two *ortho* Cl atoms are *trans* to each other, Fig. 1, whereas for 2,2′-dichlorobiphenyl they are *cis*. Thus, for these and analogous *ortho*-substituted biphenyl compounds, there should be two low-energy conformations (*cis* and *trans*); on X-ray analysis the *trans* conformation is seen here for the title compound while the *cis* is seen for 2,2′-dichlorobiphenyl. A recent study (Dynes, Baudais & Boyd, 1985) of inter-ring dihedral angles in biphenyls (including the title compound) in the gas phase from photoelectron spectroscopy found only the *cis* (or near-*syn* form) which was discussed in terms of a non-bonding attractive force between halogen atoms.

Energy refinement. In order to assess the *ortho* interactions as structural determinants, theoretical calculations were performed using two techniques available to us: (*a*) The *ab initio QM GAUSSIAN*82 method (Binkley *et al.*, 1983); (*b*) the *MM*2 molecular-mechanics method (Burkert & Allinger, 1982). The results are shown in Fig. 2. Both computational methods give qualitatively the same result; the *ortho* interactions dominate within a ±30° angle of the totally planar structures with an energy minimum near 90°. The *ab initio* potential curve has two minima, one near 75° (the lowest energy point) and one near 105°, with a very small barrier of $\simeq$0·42 kJ mol^{-1} between ($\sim$90°) whereas the molecular-mechanics curve has only a single minimum at 82°. The double minima shown by *QM* and not by *MM* as the phenyl planes rotate away from perpendicularity and towards coplanarity may indicate the onset of π-conjugation-energy lowering; this effect would be overcome by van der Waals repulsions at still lower dihedral angles. The *ab initio* results are consistent with our earlier study (McKinney, Gottschalk & Pedersen, 1983) on a series of *ortho*- and non-*ortho*-substituted biphenyls in which 2,2′-dichlorobiphenyl was found to have a minimum near 90°. The corresponding X-ray minimum occurs at 58°; however, only $\simeq$0·84 kJ mol^{-1} separate the X-ray and *ab initio* minima. Thus a wide range of dihedral angles is thermally accessible to the molecule. If $RT \simeq 2\cdot5$ kJ mol^{-1}, the accessible *ab initio* dihedral-angle

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* Lists of structure factors, anisotropic thermal parameters and least-squares-planes' details have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42940 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

* See previous footnote.

range is ~55–~110° and the accessible molecular-mechanics dihedral-angle range is ~65–~105°. This range of dihedral angles would include both *cis* and *trans* arrangements of the 2,2′-*ortho*-Cl substituents and may reasonably account for the *ortho–trans* difference in 2,2′-dichlorobiphenyl and the title compound. Using the *MM* program *MM*2p available through the *PROPHET* system to perform complete energy-minimization calculations (preliminary calculations by H. Posner and J. McKinney) on the title compound afforded two local minima, one at 68·7° dihedral angle (*trans*) and another 99·2° (*cis*). These two structures differed in energy by only 0·84 kJ mol^{-1} with the *cis* form being lower in energy. *cis* or *trans* preference in the solid state could reflect contributions from crystal lattice forces which were not considered in the energy calculations. Thus, in this case, the *ab initio* quantum-mechanical, the molecular-mechanics and the X-ray results are in substantial agreement.

Toxicological studies of individual PCB isomers have clearly demonstrated the specificity of toxicity and inducibility of mixed-function oxidase enzymes (*i.e.* cytochrome P-448 or P-450) with respect to chlorine substitution patterns (McKinney, Chae, McConnell & Birnbaum, 1985). The simplest PCB inducer of cytochrome P-448, 3,3′,4,4′-tetrachlorobiphenyl, which is also considered a toxic PCB, has a molecular structure consistent with requirements for binding the postulated receptor for induction, including an energy barrier favorable to achievement of coplanarity of the biphenyl rings (McKinney & Singh, 1981; McKinney *et al.*, 1983). Addition of Cl atoms at both *ortho* positions, as in 2,2′,4,4′,5,5′-hexachlorobiphenyl, results in preferential induction of cytochrome P-450 and a remarkably reduced toxicity. A theoretical model for the postulated receptor for induction has recently been developed based on molecular parameters and molecular-mechanics considerations with PCB's (McKinney, Darden, Lyerly & Pedersen, 1985). The important element in the model appears to be the availability of an accessible planar face which can undergo a dispersive (stacking) interaction with a receptor. Because of the noncoplanarity of the rings in *ortho*-substituted PCB's, the model predicts a greater average separation distance in their stacking interaction with the receptor. The results of this complete study with the 2,2′,4,4′,5,5′-hexachlorobiphenyl further suggest the use and importance of the theoretical approach for assessing the *ortho* effect.

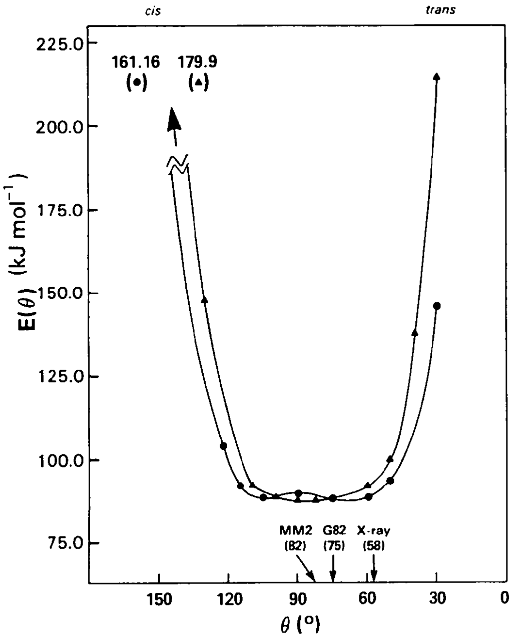

Fig. 2. Comparison of the *ab initio* (*GAUSSIAN*82) and molecular-mechanics potential-energy curves. The *ab initio* curve, established by calculations at 15° intervals. was adjusted by adding to each point the energy of the lowest *MM*2 point (87·76 kJ mol^{-1} at 82°). (●) *G*82 STO-3G; (▲) *MM*$_2$ (constrained).

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