

**SEMIEMPIRICAL MOLECULAR ORBITAL PROPERTIES AND
X-RAY STRUCTURAL STUDIES OF CHLORINATED DIPHENYL
ETHERS AND SOME RELATED COMPOUNDS SUCH AS DIOXINS**

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INTRODUCTION

Polychlorinated diphenyl ethers (PCDEs) have been identified as impurities in technical chlorophenol preparations¹. They are known to bioaccumulate and have been found in mussels² and fish samples³, avian tissues and eggs⁴, human adipose tissue⁵, finnish salmon and eagle samples and also as emissions from municipal waste incinerators⁶. Recent studies have shown that PCDEs cause immunotoxicity and induce AHH and EROD activity in C57BL/6 mice⁷. Their structural resemblance with dibenzodioxins has been suggested to cause their toxicity by same mechanisms as dibenzodioxins. The basic difference between diphenylethers and dibenzodioxins, however, is in their rigidity. Being conformationally non-rigid and sterically hindered compounds diphenylethers can not be fully planar in contrast to the structure of dibenzodioxins. Based on the X-ray crystal structure determinations⁸ of polychlorinated diphenylethers as well as their NMR spectral properties in solution state⁹, the twist angle between benzene rings is clearly dependent on the degree and arrangement of chlorine substitution.

In order to relate the structural and electronic properties of diphenylethers with their toxic properties, molecular orbital (MO) methods provide useful approaches. Although the *ab initio* MO methods are superior in comparison with approximative semiempirical MO calculations, their greatest drawback is their enormous demand for CPU time and memory size. For polychlorinated aromatics, *ab initio* MO methods practically are too slow and cumbersome to be used as an aid in predicting their properties.

In the present work, a semiempirical MO method using the AM1 hamiltonian¹⁰ was selected in calculating the structural and electronic properties of diphenylether and some related compounds *viz.* eight PCDEs with known toxic properties⁷ (presented in fig 1.) as well as dibenzodioxin and its super toxic 2,3,7,8-tetrachlorinated derivative, TCDD. AM1 approach has previously shown to possess some predicting power in estimating the mutagenic activity of chlorinated pentacyclic lactones such as MX¹¹.

RESULTS AND DISCUSSION

The atomic charges for dibenzodioxin, 2,3,7,8-TCDD, diphenylether, 3,3',4,4'-tetrachlorodiphenyl ether and 2,2',4,4',5,5'-hexachlorodiphenyl ether are presented in Figure 1. and their HOMO and LUMO energies are given in Table 1. Diphenyl ethers have been suggested to have four different conformational forms: planar, 'butterfly', skew and twist. The X-ray studies have shown that PCDEs are very strongly twisted being almost perpendicular, the inter-ring angle being 82° . The corresponding angle in 2,2',4,4'-dichlorodiphenyl ether is 68.4° , in 2,2',3,4,4',5'-hexachlorodiphenyl ether⁸ 85.5° and in 3,3',4,4'-tetrachlorodiphenyl ether¹² 73.2° , respectively. A surprising observation that an *ortho*-substituted compound *viz.* 2,4-dichloroderivative, has a smaller twist angle than 3,4-dichloro compound is explained by the packing forces such as π -electron overlaps between adjacent molecules effecting in the crystalline state. In trichlorinated rings, however, the inter-ring twist angle is greater than in dichlorinated ones as expected. This means, that increasing number of chlorine substituents reflects as increasing intra- and inter-ring steric repulsions and an increasing tendency in the inter-ring twist angle. Further this twist angle can be related with the toxic properties of these compounds, since 3,3',4,4'-tetrachloro-diphenyl ether has reported to be clearly more toxic than its di-*ortho*chlorinated derivative 2,2',4,4',5,5'-tetrachlorodiphenyl ether.

One should, however, be careful in deriving conclusions about toxicity and biological activity based alone on X-ray crystal structural data, because the crystal packing forces can play a remarkable role in the preferred conformations of flexibel compounds such as diphenylethers and biphenyls (in gaseous phase diphenyl the inter-ring twist angle is ca. 35° , but in crystalline state 0°).

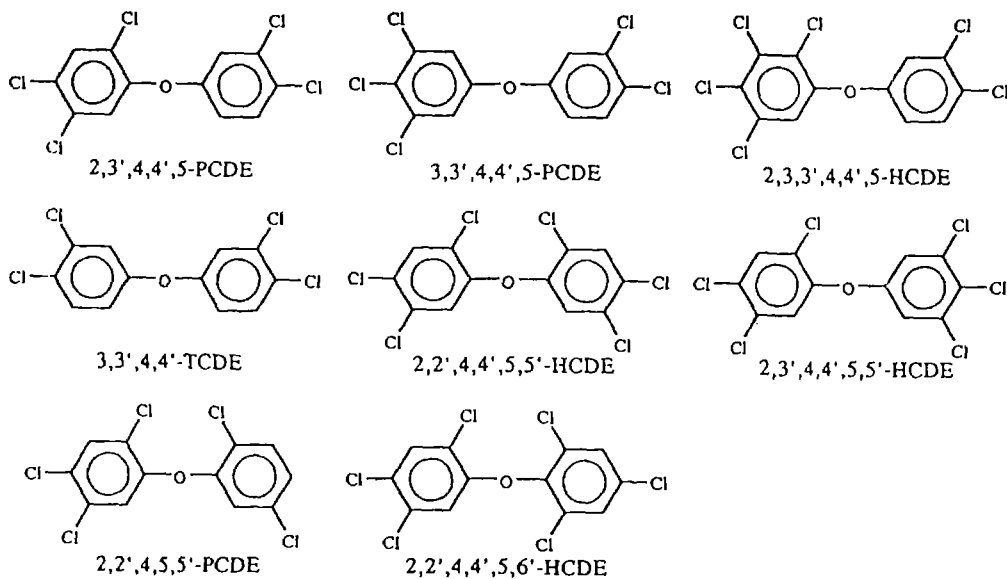


Figure 1. Structures of eight PCDE congeners with known toxic properties⁷.

Compound	E_{HOMO}	E_{LUMO}
dibenzodioxin	-8.576	-0.138
2,3,7,8-TCDD	-8.998	-0.909
diphenylether	-9.539	0.192
3,3',4,4'-TCDE	-9.286	-0.578
2,2',4,4',5,5'-HCDE	-9.701	-0.794

Table 1. The calculated HOMO and LUMO energies for dibenzodioxin, 2,3,7,8-TCDD, diphenylether, 3,3',4,4'-tetrachlorodiphenyl ether and 2,2',4,4',5,5'-hexachlorodiphenyl ether in electron volts.

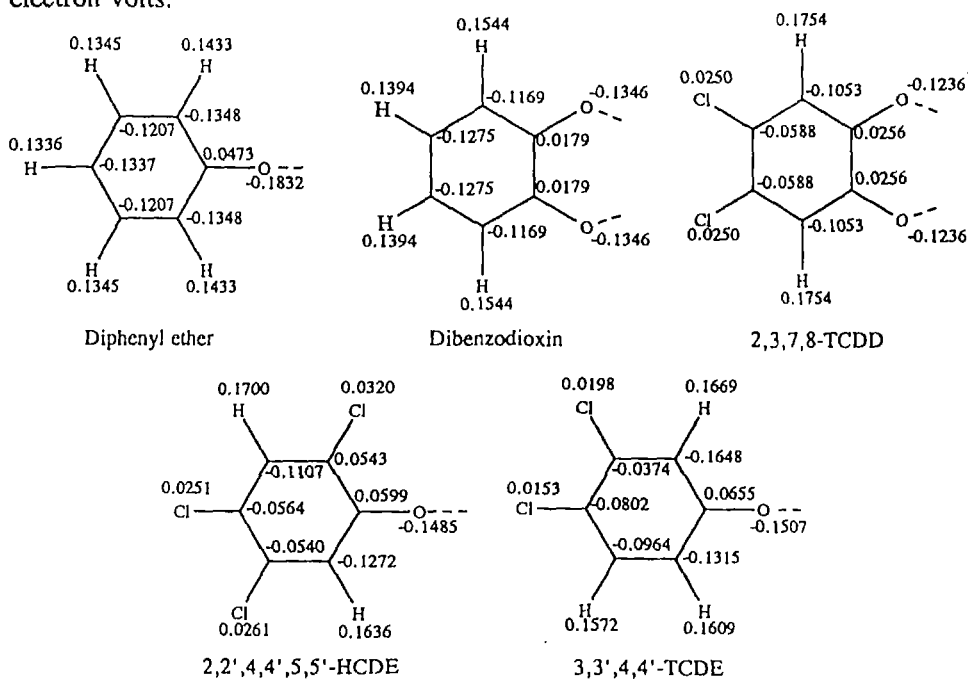


Figure 2. Atomic charges for dibenzodioxin, 2,3,7,8-TCDD, diphenylether, 3,3',4,4'-tetrachlorodiphenyl ether and 2,2',4,4',5,5'-hexachlorodiphenyl ether calculated by AM1 semiempirical method.

EXPERIMENTAL

The semi-empirical RHF/AM1 molecular orbital calculations⁹ have been performed in a Silicon Graphics WorkStation using a personal Iris system and a Spartan program package. X-ray studies were performed by Efran-Nonius, CAD-4 diffractometer using VAX 3100 computer and shelx, crystals and shakal programs. Chlorinated diphenyl ethers were synthesized by known method¹³. Crystals of PCDEs for X-ray studies were grown by slow evaporation of a concentrated ethanol solution.

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