

SEMIEMPIRICAL QUANTUM MECHANICAL QUANTITATIVE STRUCTURE ACTIVITY
RELATIONSHIPS FOR TCDD AND COPLANAR PCBs.

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ABSTRACT

A Quantitative Structure Activity Relationship between published AHH induction data and electronic charge distribution, calculated using the AM1 Hamiltonian is established for 2,3,7,8-TCDD, and ten non-ortho and mono-ortho coplanar PCB congeners, linear regression correlation coefficient $(r) = 0.9504$. The relationship of rotational barriers and Ah receptor binding for non-ortho and mono-ortho PCBs is also investigated and preliminary results presented.

INTRODUCTION

The evidence that toxic halogenated aromatic hydrocarbons exhibit a common biological toxic response, related to aryl hydrocarbon hydroxylase (AHH) induction, mediated by the aryl hydrocarbon (Ah) receptor (1), suggests that the Structure Activity Relationships observed could be based on specific electronic properties of the molecular structures. A Quantitative Structure Activity Relationship relating Ah binding data to parameters of polarizability for PCBs has previously been established (6), and it has recently been proposed that a more positive charge distribution at the site of hydroxylation may facilitate the oxidative metabolism of PCBs (3).

The parametric semiempirical quantum mechanical model AM1 (2) provides a method capable of calculating molecular electronic charge distribution and enthalpies of formation for the halogenated aromatic hydrocarbons with reasonable computational resources. Ab initio quantum mechanical methods, which calculate molecular properties using only fundamental physical constants, in comparison require much greater resources.

METHODOLOGY

The MOPAC 5.0 program (4) was used to obtain fully energy minimised structures using the AM1 method, within the structural constraints described below. The set of PCB congeners used were

the non-ortho and mono-ortho coplanar PCBs for which experimental data for in vitro AHH induction and cytosol Ah binding was available (1). 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) was included as a model Ah receptor binding compound. All PCB structures were minimised with the aromatic rings constrained in a planar configuration, on the assumption that coplanar PCBs form a planar binding complex with the Ah receptor. 3,3' substituted PCBs were minimised in the anti conformation to maximise coplanarity with 2,3,7,8-TCDD.

A potential active site for each congener was selected for each congener by taking the most positively charged carbon atom bearing a hydrogen substituent (Table 1.). The values of $\log_{10}(EC_{50})$ for AHH enzyme induction (Rat hepatoma H-4-II E cells in vitro (1,5)) were plotted against active site charge (q) and linear regression analysis performed (Figure 1.). The charge values determined directly from the AM1 wavefunction were used (calculated from the trace of the density matrix over all basis orbitals for a specific atom X, i.e. $q_x = Z_x - \sum_{\mu}^x P_{\mu\mu}$ (8)).

In order to investigate the constraints on planar binding of PCBs to the Ah receptor, barriers to rotation were investigated by calculating the heats of formation using AM1 for a series of minimised structures where the dihedral angle between the aromatic rings was varied from 0° to 180°. Biphenyl and

2-chlorobiphenyl (figure 2.) were used as model compounds.

RESULTS

Table 1.

	C-site	PCB	charge q (e)	AHH Ind. EC ₅₀ (M)	Ah bind. K _b (M)
2378-tcdd			-0.1052	7.2 x 10 ⁻¹¹	1.0 x 10 ⁻⁸
3,3',4,4'-tetraCB	2	77	-0.1085	3.5 x 10 ⁻⁸	4.3 x 10 ⁻⁸
3,3',4,4',5-pentaCB	2	126	-0.1063	2.4 x 10 ⁻¹⁰	6.0 x 10 ⁻⁸
3,3',4,4',5,5'-hexaCB	2	169	-0.1089	6.0 x 10 ⁻⁸	NA
2,3,3',4,4'-pentaCB	6	105	-0.1083	8.8 x 10 ⁻⁸	4.3 x 10 ⁻⁶
2,3',4,4',5-pentaCB	6'	118	-0.1105	1.2 x 10 ⁻⁵	9.1 x 10 ⁻⁵
2,3,3',4,4',5-hexaCB	2	156	-0.1093	2.1 x 10 ⁻⁶	7.1 x 10 ⁻⁶
2,3,3',4,4',5'-hexaCB	6'	157	-0.1112	1.1 x 10 ⁻⁵	5.0 x 10 ⁻⁶
2,3,4,4',5-pentaCB	2'	114	-0.1099	9.7 x 10 ⁻⁷	4.7 x 10 ⁻⁶
2',3,4,4',5-pentaCB	6'	123	-0.1095	3.9 x 10 ⁻⁶	1.4 x 10 ⁻⁵
2,3',4,4',5,5'-hexaCB	6	167	-0.1095	1.3 x 10 ⁻⁵	1.6 x 10 ⁻⁵

Induction and binding data from references (1,5).

Linear regression fit for AHH induction on active site charge.

Correlation Coeff. (r) 0.9504
 $\log_{10}(\text{EC}_{50}) = 1001.2(q) + 115.63$

Linear regression fits excluding PCB 169 for which experimental Ah binding is data not available.

AHH Induction on q

Correlation Coeff. (r) 0.956597

$$\log_{10}(K_b) = 591.27(q) + 70.08$$

Ah Binding on q

Correlation Coeff. (r) 0.834939

$$\log_{10}(EC_{50}) = 1002.8(q) + 1115.75$$

AHH Induction on Ah binding

Correlation Coeff. (r) 0.91172

$$\log_{10}(EC_{50}) = 1.3497(\log_{10}(K_b)) - 1.137$$

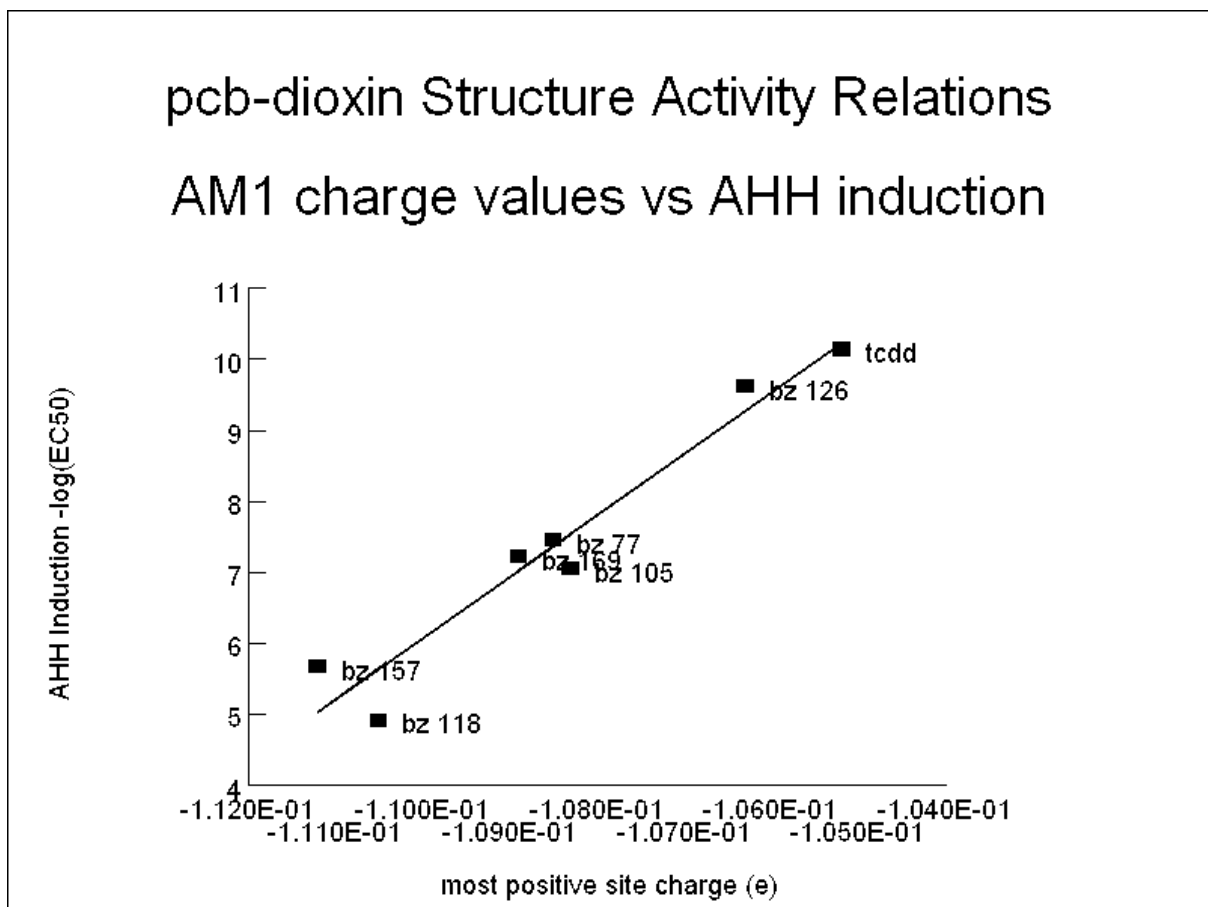


Figure 1.

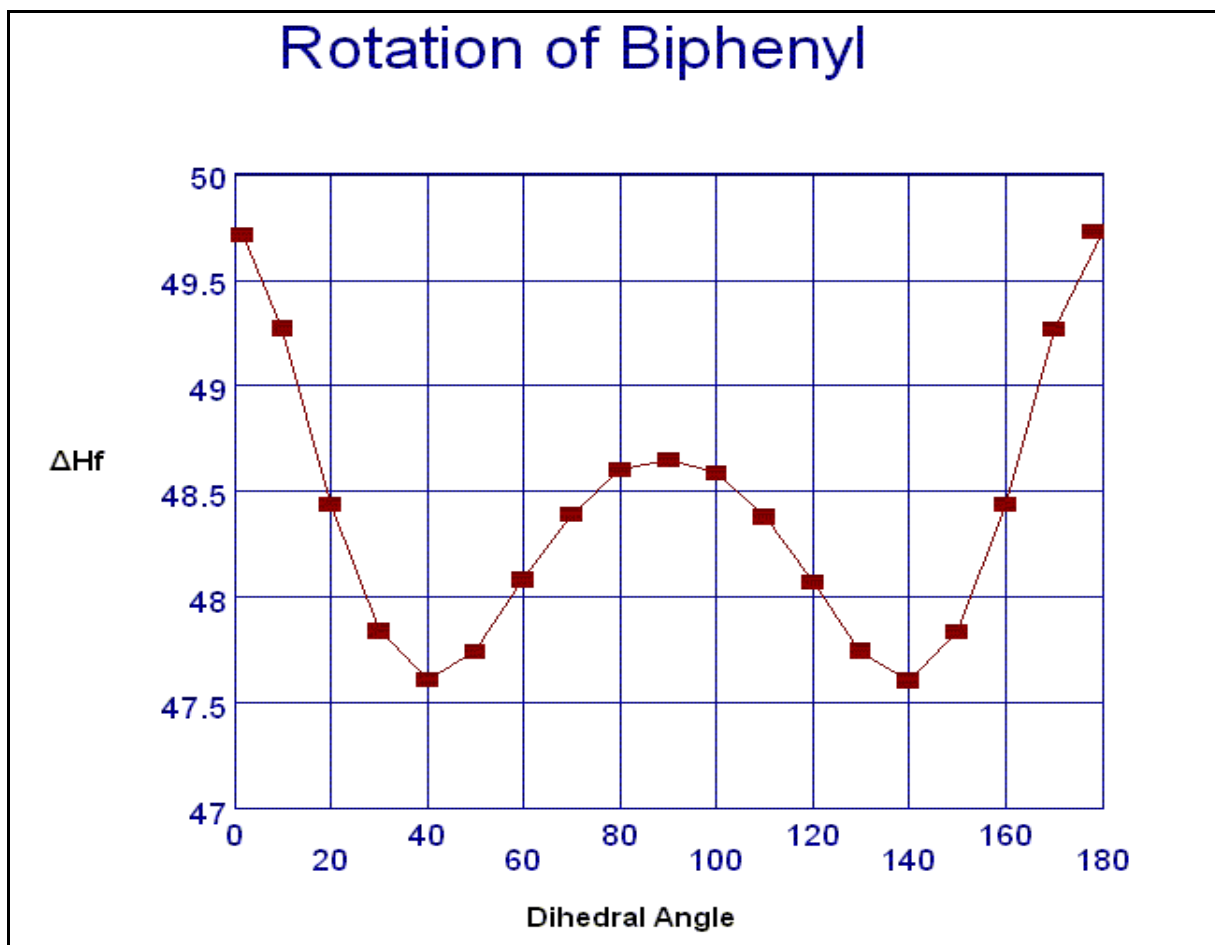


Figure 2.

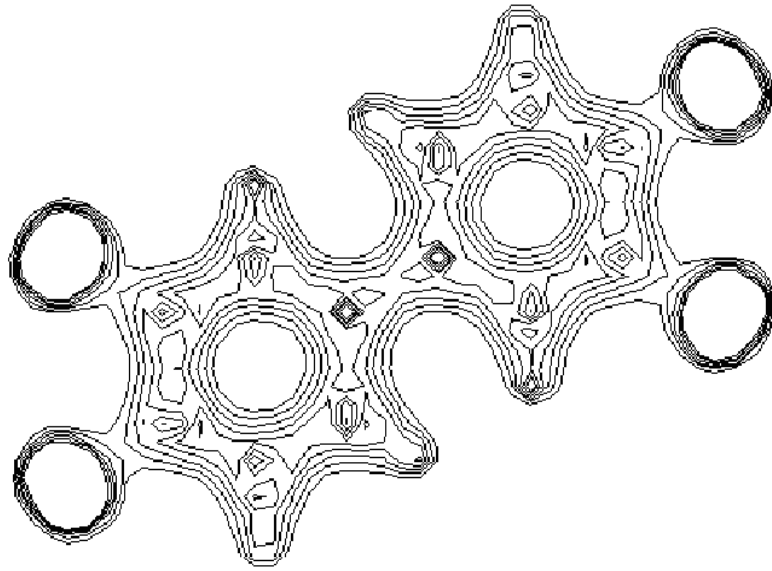
DISCUSSION

The enthalpic barriers to rotation for biphenyl and 2-chlorobiphenyl were calculated to be approx. 2.1 kcal mol⁻¹ and 7.1 kcal mol⁻¹ respectively (figure 2.). Previously the rotational barriers for PCBs have been estimated in an ab initio calculation (7) using the STO-3G minimal Gaussian basis set. Values of approx. 3.7 kcal mol⁻¹ and 48.9 kcal mol⁻¹ for biphenyl and 2,3'-dichlorobiphenyl respectively were reported. The strongest binding of a chloroaryl hydrocarbon to the Ah receptor is $K_d \sim 10^{-8}$ M. which thermodynamically indicates a free energy of

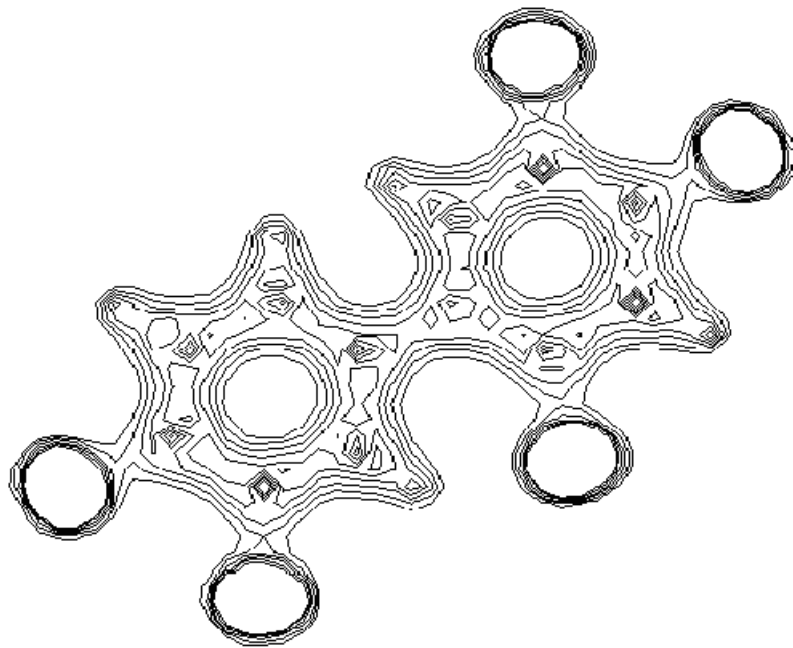
binding $\Delta G = -10.9 \text{ kcal mol}^{-1}$ which must provide the upper limit for any rotational barrier that will allow Ah receptor binding to occur if a planar configuration is required, as is probable since the other major ligands are all planar molecules (PAHs, PCDDs, PCDFs). Since mono-ortho substituted PCBs have values of $K_d \sim 10^{-4}$ to 10^{-6} M. , the ab initio STO-3G rotational barrier for mono-ortho substituted PCBs is therefore high and the AM1 calculation is more consistent with the experimental data.

The correlation coefficient for AHH induction dependence on site charge significantly higher than for that of Ah receptor binding on site charge. This suggests that induction may involve two partially separate processes; binding and recognition of electronic charge distribution. Possibly small differences in charge distribution on the aromatic ring can increase the probability, of the receptor conformationally realigning itself into a form capable, of initiating the process of interaction with the promoter regions of the DNA coding for the enzymes that are induced. The unique electron distribution about each hydrogen substituted carbon for selected planar constrained PCBs is shown in figure 3.

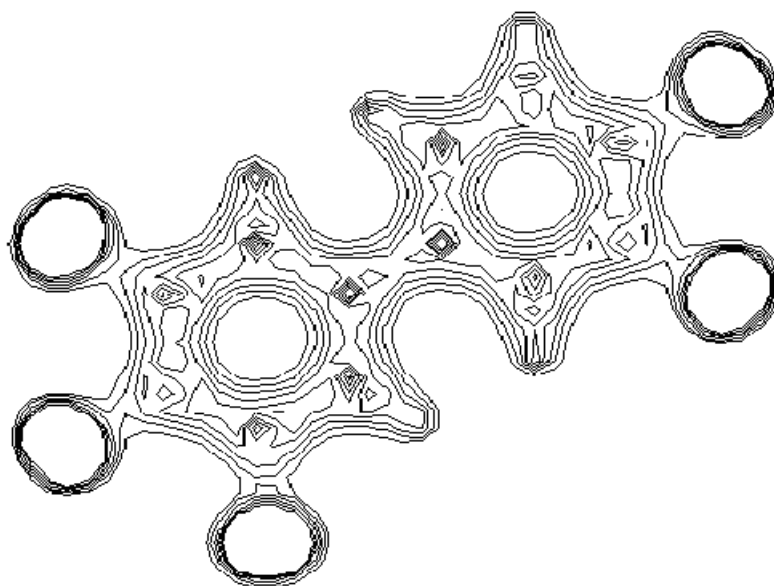
Figure (3)



(a)



(b)



(c)

ELECTRON DENSITY MAPS (AM1) of (a) 3,3',4,4'-tetraCB, (b) 2,3',4,4'5-pentaCB and (c) 3,3',4,4',5-pentaCB with contours at 0.25 intervals from 0.75 To 2 e Angstrom⁻³ lying in the molecular plane of a constrained planar configuration.

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