

Three-Dimensional Quantitative Structure–Property Relationship (3D-QSPR) Models for Prediction of Thermodynamic Properties of Polychlorinated Biphenyls (PCBs): Enthalpy of Sublimation

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Three-dimensional quantitative structure–property relationship (3D-QSPR) models have been constructed using comparative molecular field analysis (CoMFA) to correlate the sublimation enthalpies at 298.15 K of a series of polychlorinated biphenyls (PCBs) with their CoMFA-calculated physicochemical properties. Various alignment schemes, such as *atom fit*, *as is*, and *inertial* were employed in this study. Separate CoMFA models were developed using different partial charge formalisms, namely, electrostatic potential (ESP) and Gasteiger-Marsili (GM) charges. Among the four different CoMFA models constructed for sublimation enthalpy ($\Delta_{\text{sub}}H_{\text{m}}(298.15 \text{ K})$), the model that combined *atom fit* alignment and ESP charges yielded the greatest self-consistency ($r^2 = 0.976$) and internal predictive ability ($r_{\text{cv}}^2 = 0.750$). This CoMFA model was used to predict $\Delta_{\text{sub}}H_{\text{m}}(298.15 \text{ K})$ of PCBs for which the corresponding experimental values are unavailable in the literature.

INTRODUCTION

Polychlorinated biphenyls (PCBs), a class of persistent organic chemicals, have attracted the attention of scientists in recent years. Due to their remarkable insulating capacity and flame resistant nature, PCBs replaced combustible insulating fluids in capacitors and transformers and reduced the risk of fire in hospitals, schools, and factories. PCBs entered the environment as components of pesticides, plasticizers, and adhesives. The nonflammability and chemical stability of PCBs have contributed to the widespread environmental problems associated with these organohalogen compounds. The lipophilicity of these compounds is responsible for their accumulation in the food chain and the cause of adverse human health effects.

Several computational methods have been developed and applied to estimate the physicochemical properties of PCBs, for example, their *n*-octanol/water partition coefficients,¹ gas chromatographic retention times,^{2,3} relative heats of formation,⁴ and lipophilicity, electron affinities, and entropies.⁵ Quantitative structure–activity relationship (QSAR) models and comparative molecular field analysis (CoMFA), a three-dimensional QSAR (3D-QSAR) paradigm, are based on the assumption that most intermolecular interactions are non-covalent and shape-dependent.⁶ CoMFA has been used to examine estrogen receptor binding affinities of polychlorinated hydroxybiphenyls,⁷ to estimate the binding affinity of PCBs to the aryl hydrocarbon receptor,⁸ and to identify the PCB isomers responsible for induction of cytochrome P-448 and P-450.⁹

The aim of this study was to use CoMFA for deriving three-dimensional quantitative structure–property relationship (3D-QSPR) models in order to establish a correlation between the sublimation enthalpies of PCBs at 298.15 K ($\Delta_{\text{sub}}H_{\text{m}}(298.15 \text{ K})$) and the CoMFA-generated steric and electrostatic fields surrounding the PCB molecules. The sublimation enthalpy, $\Delta_{\text{sub}}H_{\text{m}}(298.15 \text{ K})$, is an experimental measure of the intermolecular forces that lead to the specific packing observed in the solid state of crystalline materials.¹⁰ It is an important property of the solid state that can serve a variety of useful purposes, such as calculation of enthalpies of formation in the condensed phase and establishment of a quantitative relationship between vapor pressure and temperature using the Clausius–Clapeyron equation.¹⁰

Alignment Schemes. The present study investigates various alignment schemes and partial charge formalisms for the development of predictive models for the sublimation enthalpies of PCBs at 298.15 K. The structural alignment of molecules is a crucial input variable in the development of a CoMFA model since the relative interaction energies depend on the relative molecular positions.

Atom fit alignment of molecules performs a least-squares fit between two molecules by matching pairs of atoms. The quality of the fit is denoted by the root-mean-square deviation (RMSD) value computed for the matched atoms.¹¹ The *as is* option in the *Database Align* module in SYBYL 6.7 molecular modeling software (Tripos, Inc., St. Louis, MO) has been used to align PCBs to the biphenyl template. This alignment scheme does not change the orientation of the molecules. *Inertial* alignment of PCBs to the biphenyl template, in which only carbon atoms of the biphenyl ring were considered for alignment, was also performed in SYBYL. Partial atomic charges derived from both the calculated ESP and the Gasteiger-Marsili (GM) methods have

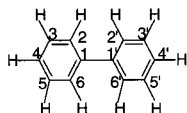
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Table 1. Summary of Statistical Results from CoMFA-PLS Analysis of Sublimation Enthalpies ($\Delta_{\text{sub}}H_m(298.15 \text{ K})$) of 15 PCBs in the Training Set Using Different Alignment Schemes and Partial Charge Formalisms

alignment scheme, partial charge formalism	<i>atom fit</i> , ESP ^a	<i>atom fit</i> , GM ^b	<i>inertial</i> , ESP ^a	<i>as is</i> , ESP ^a
cross-validated r^2 (r_{cv}^2)	0.755 (0.750) ^c	0.710 (0.730)	0.539 (0.462)	0.731 (0.740)
conventional r^2	0.977 (0.976)	0.845 (0.856)	0.990 (0.979)	0.992 (0.989)
standard error of estimate (in kJ/mol)	2.27 (2.24)	5.43 (4.90)	1.75 (2.31)	1.56 (1.67)
principal components	3 (4)	1 (1)	6 (6)	6 (6)
F values	156 (121)	70.9 (88.9)	134 (76.4)	168 (147)

^a Electrostatic potential. ^b Gasteiger-Marsili. ^c The values in parentheses represent the statistical results for the original data set of 17 PCBs.

**Figure 1.** Atoms C1, C2, C4, and C5 of the biphenyl template were selected for *atom fit* alignment of PCB molecules.

been used in conjunction with *atom fit* alignment of molecules.

METHODOLOGY

The molecular modeling and CoMFA computations were performed on a Silicon Graphics Inc. (SGI) Indy workstation and IRIX (version 6.2) operating system. The molecules in the data set were constructed using SYBYL 6.5 molecular modeling software (Tripos, Inc., St. Louis, MO). All molecules were geometry optimized by implementing the Merck molecular force field (MMFF94) with a distance dependent dielectric function ($\epsilon = \epsilon_o r$, with $\epsilon_o = 1$) until the convergence criterion of 0.004184 kJ/mol (0.001 kcal/mol) change in energy between successive iterations was achieved.

A study by Mulholland⁴ evaluated three semiempirical methods to calculate the rotational barriers and preferred conformations of biphenyl. This study showed that, compared to MNDO (modified neglect of diatomic overlap) and PM3 (parametric method 3), AM1 (Austin model 1) proved to be most accurate in estimating the optimal dihedral angle and rotational energy barriers for biphenyl, with results comparable to experimental observations and ab initio calculations. Consequently, the optimized structures from SYBYL were used as initial coordinates for AM1 geometry optimization in SPARTAN (Version 5.0.1, Wavefunction, Inc., Irvine, CA). The conformational space about the twist bond connecting the two ring systems was systematically explored by changing the dihedral angle from 0° to 360° through 25 steps (i.e., 14.4° increments). The lowest energy conformer obtained from this search was subjected to an AM1 geometry optimization. Partial atomic charges were computed using the electrostatic potential (ESP) utility in SPARTAN.

Data Set. The data set of 17 compounds consisted of a biphenyl molecule and 16 PCBs. This data set was divided into a training set of 15 compounds and a test set of two PCBs. It is customary for the test set to comprise about 10% of the total number of compounds in the data set. Isomers 18 (2,2',5-trichlorobiphenyl) and 52 (2,2',5,5'-tetrachlorobiphenyl) were selected as the test set since these compounds are representative of the trichlorobiphenyl and tetrachlorobiphenyl homologs.

With the exception of biphenyl, the sublimation enthalpies of PCBs at 298.15 K are unavailable in the literature. However, the values of sublimation enthalpies at tempera-

tures other than 298.15 K have been reported. These values, which were usually measured over a temperature range, were adjusted to 298.15 K using the following equation:¹⁰

$$\Delta_{\text{sub}}H_m(298.15 \text{ K}) = \Delta_{\text{sub}}H_m(T_{\text{mean}}) + [0.75 + 0.15\{Cp_{\text{cestd}}(298.15 \text{ K})\}]\{T_{\text{mean}} - 298.15\}$$

The term T_{mean} represents the mean temperature of measurement. The value of the heat capacity of the solid phase, $Cp_{\text{cestd}}(298.15 \text{ K})$, was estimated using a group additivity method.¹²

In those cases where experimental values have not been measured, the sublimation enthalpies at 298.15 K were calculated from the sum of the fusion enthalpies ($\Delta_{\text{fus}}H_m(298.15 \text{ K})$) and vaporization enthalpies ($\Delta_{\text{vap}}H_m(298.15 \text{ K})$). The vaporization enthalpies of PCBs at 298.15 K have been determined by Puri et al.¹³ using correlation gas chromatography. The fusion enthalpies of PCBs at the melting point ($\Delta_{\text{fus}}H_m(T_{\text{fus}})$) have been reported in the literature. These values were adjusted to 298.15 K using the following equation:¹⁰

$$\Delta_{\text{fus}}H_m(298.15 \text{ K}) = \Delta_{\text{fus}}H_m(T_{\text{fus}}) + [0.75 + 0.15\{Cp_{\text{cestd}}(298.15 \text{ K})\}]\{T_{\text{fus}} - 298.15\} + [10.58 + 0.26\{Cp_{\text{lestd}}(298.15 \text{ K})\}]\{298.15 - T_{\text{fus}}\}$$

The values of the heat capacity of the solid and liquid phase, $Cp_{\text{cestd}}(298.15 \text{ K})$ and $Cp_{\text{lestd}}(298.15 \text{ K})$, respectively, were estimated using a group additivity method.¹²

Alignment Schemes. Biphenyl was chosen as the template molecule for the various alignment schemes implemented in this study. For *atom fit* alignment, PCB molecules were aligned via RMSD fit of atoms C1, C2, C4, and C5 to the corresponding atoms on the biphenyl ring (Figure 1). These atoms were selected to consider the *ortho* (C2), *meta* (C5), and *para* (C4) positions on the benzene ring and the atom (C1) connected to the carbon atom of the second benzene ring.

Inertial and *as is* alignment schemes were also used to align PCB compounds to the biphenyl template. *Atom fit* alignment was used to study the effect of partial atomic charges on the sublimation enthalpy of PCBs. The ESP charges were imported from SPARTAN and Gasteiger-Marsili (GM) charges were computed in SYBYL.

After alignment of the molecules in the data set, each PCB molecule was placed in the center of a regularly spaced grid of 2.0 Å dimensions in x, y, and z directions. The steric (van der Waals/Lennard-Jones 12–6 function) and electrostatic (Coulombic) potential energy fields were calculated separately at each grid point of the three-dimensional lattice by

Table 2. Comparison of Experimental and CoMFA-Predicted Values (*Atom Fit* Alignment, ESP Charges) of Sublimation Enthalpy ($\Delta_{\text{sub}}H_m(298.15 \text{ K})$ in kJ/mol) for the Model Constructed Using the Original Data Set of 17 PCBs

IUPAC no.	compounds	experimental	predicted	residual ^a
	biphenyl	82.1 ^b	85.0	-2.9
1	2-monochlorobiphenyl	86.3 ^{c,d}	84.6	1.7
3	4-monochlorobiphenyl	82.4 ^{c,e}	83.2	-0.8
4	2,2'-dichlorobiphenyl	96.9 ^f	98.1	-1.2
15	4,4'-dichlorobiphenyl	105.1 ^f	103.6	1.5
18	2,2',5-trichlorobiphenyl	99.5 ^{c,g}	97.3	2.2
29	2,4,5-trichlorobiphenyl	103.6 ^{c,h}	103.7	-0.1
30	2,4,6-trichlorobiphenyl	95.6 ^{c,h}	93.9	1.7
49	2,2',4,5'-tetrachlorobiphenyl	108.3 ^{c,e}	107.4	0.9
52	2,2',5,5'-tetrachlorobiphenyl	101.0 ^{c,i}	103.1	-2.1
53	2,2',5,6'-tetrachlorobiphenyl	101.0 ^{c,g}	101.4	-0.4
101	2,2',4,5,5'-pentachlorobiphenyl	109.8 ^{c,j}	109.1	0.7
128	2,2',3,3',4,4'-hexachlorobiphenyl	122.7 ^{c,j}	124.9	-2.2
155	2,2',4,4',6,6'-hexachlorobiphenyl	101.5 ^{c,j}	103.0	-1.5
171	2,2',3,3',4,4',6-heptachlorobiphenyl	122.7 ^{c,j}	118.7	4.0
202	2,2',3,3',5,5',6,6'-octachlorobiphenyl	114.2 ^{c,j}	113.3	0.9
209	2,2',3,3',4,4',5,5',6,6'-decachlorobiphenyl	119.1 ^{c,k}	121.6	-2.5

^a The residual is the difference between experimental and CoMFA-predicted values of sublimation enthalpy ($\Delta_{\text{sub}}H_m(298.15 \text{ K})$). ^b Average of the values from refs 16–20 was used. ^c Fusion enthalpy at the melting point ($\Delta_{\text{fus}}H_m(T_{\text{fus}})$) was adjusted to 298.15 K using the following equation:¹⁰ $\Delta_{\text{fus}}H_m(298.15 \text{ K}) = \Delta_{\text{fus}}H_m(T_{\text{fus}}) + [0.75 + 0.15\{Cp_{\text{cestd}}(298.15 \text{ K})\}]\{T_{\text{fus}} - 298.15\} + [10.58 + 0.26\{Cp_{\text{lestd}}(298.15 \text{ K})\}]\{298.15 - T_{\text{fus}}\}$. The values of the heat capacity of the solid and liquid phase, $Cp_{\text{cestd}}(298.15 \text{ K})$ and $Cp_{\text{lestd}}(298.15 \text{ K})$ respectively, were estimated using a group additivity method.¹² ^d Fusion enthalpy from ref 21 was adjusted to 298.15 K and added to vaporization enthalpy ($\Delta_{\text{vap}}H_m(298.15 \text{ K})$) from ref 13. ^e Fusion enthalpy from ref 22 was adjusted to 298.15 K and added to vaporization enthalpy ($\Delta_{\text{vap}}H_m(298.15 \text{ K})$) from ref 13. ^f From ref 23. A plot of $\log(p/\text{Pa})$ against $(1/T/\text{K})$ for the solid phase was used to calculate the enthalpy of sublimation from the product of the slope of the plot and the gas constant, $R = 8.314 \text{ J/K mol}$. The sublimation enthalpy at the mean temperature, T_{mean} , was adjusted to 298.15 K using the following equation:¹⁰ $\Delta_{\text{sub}}H_m(298.15 \text{ K}) = \Delta_{\text{sub}}H_m(T_{\text{mean}}) + [0.75 + 0.15\{Cp_{\text{cestd}}(298.15 \text{ K})\}]\{T_{\text{mean}} - 298.15\}$. The value of the heat capacity of the solid phase, $Cp_{\text{cestd}}(298.15 \text{ K})$, was estimated using a group additivity method.¹² ^g Fusion enthalpy at the melting point was determined in this study using differential scanning calorimetry (DSC). This value was adjusted to 298.15 K and added to vaporization enthalpy from ref 13. ^h Fusion enthalpy from ref 24 was adjusted to 298.15 K. Vaporization enthalpies from ref 25 were adjusted to 298.15 K using the vaporization enthalpies of eicosane at 298.15 K from ref 26. ⁱ The fusion enthalpy at the melting point for this compound was determined from the product of the entropy of fusion from ref 27 and the melting point of the compound. This value was adjusted to 298.15 K. Vaporization enthalpy from ref 25 was adjusted to 298.15 K as described in *h*. ^j Fusion enthalpy from ref 22 was adjusted to 298.15 K. Vaporization enthalpy from ref 25 was adjusted to 298.15 K as described in *h*. ^k Fusion enthalpy from ref 24 was adjusted to 298.15 K. Vaporization enthalpy from ref 25 was adjusted to 298.15 K as described in *h*.

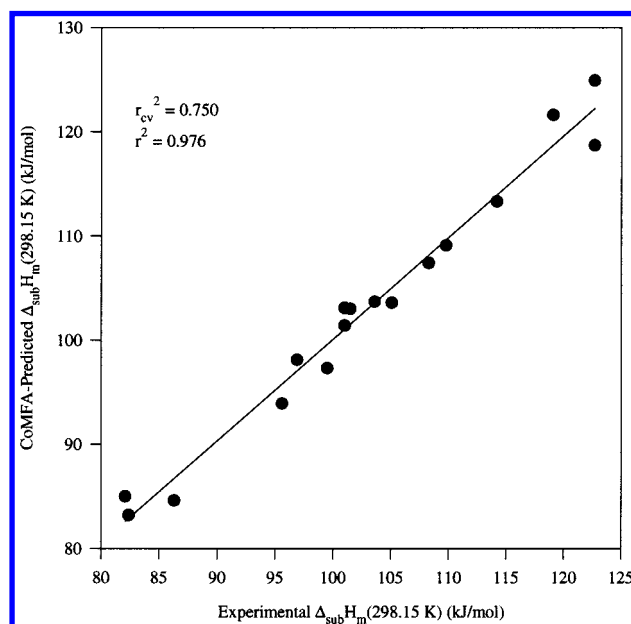
summing the individual energy interactions between each atom of the PCB molecule and a probe consisting of a sp^3 hybridized carbon atom with +1 charge. A distance-dependent dielectric function was applied, and values of the steric and electrostatic energies were truncated at 125 kJ/mol.

Partial Least Squares (PLS) Analysis. Partial least squares (PLS),¹⁴ a widely used regression technique, expresses a dependent variable (target property) in terms of linear combinations of the independent variables (descriptor data). All calculations were performed using the QSAR module in SYBYL. The QSPR table was constructed with rows containing values of $\Delta_{\text{sub}}H_m(298.15 \text{ K})$ for each compound in the data (training) set as the dependent variable, and the columns contained the steric and electrostatic fields as the independent variables.

An initial PLS analysis was performed using the “leave-one-out” cross validation procedure to determine the optimum number of latent variables (more commonly known as principal components or PCs) required for the subsequent analysis of data. The optimum number of PCs is that which yields the largest cross-validated r^2 (r_{cv}^2) value. The PLS analysis was repeated without cross-validation using the optimum number of components. This final analysis yielded a predictive model and associated conventional r^2 values.

RESULTS AND DISCUSSION

The statistical results of the CoMFA analysis using different alignment and partial atomic charge schemes are

**Figure 2.** A plot of CoMFA-predicted (*atom fit* alignment, ESP charges) versus experimental values of sublimation enthalpies ($\Delta_{\text{sub}}H_m(298.15 \text{ K})$) for the 17 PCBs in the original data set.

summarized in Table 1. The model constructed using *atom fit* alignment with ESP charges demonstrated the best internal predictive ability for the sublimation enthalpy of PCBs at 298.15 K. This model, which consists of 15 PCBs in the training set, required three PCs to explain the variation in $\Delta_{\text{sub}}H_m(298.15 \text{ K})$ values. It yielded exceptional statistical

Table 3. CoMFA-Predicted Values of Sublimation Enthalpy ($\Delta_{\text{sub}}H_m(298.15 \text{ K})$ in kJ/mol) for 193 Untested PCBs, Using the Model (*Atom Fit* Alignment, ESP Charges) Constructed from the Original Data Set of 17 PCBs

IUPAC no.	compounds	no. of Cl atoms	no. of ortho Cl atoms	CoMFA predicted values
2	3-monochlorobiphenyl	1	0	90.7
5	2,3-dichlorobiphenyl	2	1	98.1
6	2,3'-dichlorobiphenyl	2	1	98.9
7	2,4-dichlorobiphenyl	2	1	97.8
8	2,4'-dichlorobiphenyl	2	1	100.8
9	2,5-dichlorobiphenyl	2	1	92.8
10	2,6-dichlorobiphenyl	2	2	87.4
11	3,3'-dichlorobiphenyl	2	0	90.9
12	3,4-dichlorobiphenyl	2	0	100.0
13	3,4'-dichlorobiphenyl	2	0	101.9
14	3,5-dichlorobiphenyl	2	0	91.4
16	2,2',3-trichlorobiphenyl	3	2	101.3
17	2,2',4-trichlorobiphenyl	3	2	100.4
19	2,2',6-trichlorobiphenyl	3	3	92.0
20	2,3,3'-trichlorobiphenyl	3	1	91.0
21	2,3,4-trichlorobiphenyl	3	1	93.0
22	2,3,4'-trichlorobiphenyl	3	1	106.8
23	2,3,5-trichlorobiphenyl	3	1	92.8
24	2,3,6-trichlorobiphenyl	3	2	95.5
25	2,3',4-trichlorobiphenyl	3	1	90.8
26	2,3',5-trichlorobiphenyl	3	1	94.1
27	2,3',6-trichlorobiphenyl	3	2	99.9
28	2,4,4'-trichlorobiphenyl	3	1	96.4
31	2,4',5-trichlorobiphenyl	3	1	86.9
32	2,4',6-trichlorobiphenyl	3	2	105.2
33	2',3,4-trichlorobiphenyl	3	1	96.1
34	2',3,5-trichlorobiphenyl	3	1	96.4
35	3,3',4-trichlorobiphenyl	3	0	94.7
36	3,3',5-trichlorobiphenyl	3	0	97.6
37	3,4,4'-trichlorobiphenyl	3	0	107.7
38	3,4,5-trichlorobiphenyl	3	0	100.9
39	3,4',5-trichlorobiphenyl	3	0	108.2
40	2,2',3,3'-tetrachlorobiphenyl	4	2	109.8
41	2,2',3,4-tetrachlorobiphenyl	4	2	103.9
42	2,2',3,4'-tetrachlorobiphenyl	4	2	110.3
43	2,2',3,5-tetrachlorobiphenyl	4	2	102.4
44	2,2',3,5'-tetrachlorobiphenyl	4	2	105.0
45	2,2',3,6-tetrachlorobiphenyl	4	3	96.7
46	2,2',3,6'-tetrachlorobiphenyl	4	3	94.3
47	2,2',4,4'-tetrachlorobiphenyl	4	2	104.8
48	2,2',4,5-tetrachlorobiphenyl	4	2	99.5
50	2,2',4,6-tetrachlorobiphenyl	4	3	97.0
51	2,2',4,6'-tetrachlorobiphenyl	4	3	94.4
54	2,2',6,6'-tetrachlorobiphenyl	4	4	94.8
55	2,3,3',4-tetrachlorobiphenyl	4	1	94.6
56	2,3,3',4'-tetrachlorobiphenyl	4	1	98.2
57	2,3,3',5-tetrachlorobiphenyl	4	1	102.8
58	2,3,3',5'-tetrachlorobiphenyl	4	1	101.1
59	2,3,3',6-tetrachlorobiphenyl	4	2	104.1
60	2,3,4,4'-tetrachlorobiphenyl	4	1	100.1
61	2,3,4,5-tetrachlorobiphenyl	4	1	104.0
62	2,3,4,6-tetrachlorobiphenyl	4	2	103.5
63	2,3,4',5-tetrachlorobiphenyl	4	1	102.6
64	2,3,4',6-tetrachlorobiphenyl	4	2	106.2
65	2,3,5,6-tetrachlorobiphenyl	4	2	101.1
66	2,3',4,4'-tetrachlorobiphenyl	4	1	105.1
67	2,3',4,5-tetrachlorobiphenyl	4	1	102.8
68	2,3',4,5'-tetrachlorobiphenyl	4	1	101.4
69	2,3',4,6-tetrachlorobiphenyl	4	2	104.3
70	2,3',4',5-tetrachlorobiphenyl	4	1	101.6
71	2,3',4',6-tetrachlorobiphenyl	4	2	107.5
72	2,3',5,5'-tetrachlorobiphenyl	4	1	104.0
73	2,3',5',6-tetrachlorobiphenyl	4	2	108.0
74	2,4,4',5-tetrachlorobiphenyl	4	1	103.0
75	2,4,4',6-tetrachlorobiphenyl	4	2	109.8
76	2',3,4,5-tetrachlorobiphenyl	4	1	99.8
77	3,3',4,4'-tetrachlorobiphenyl	4	0	106.0
78	3,3',4,5-tetrachlorobiphenyl	4	0	101.3
79	3,3',4,5'-tetrachlorobiphenyl	4	0	98.8
80	3,3',5,5'-tetrachlorobiphenyl	4	0	101.6
81	3,4,4',5-tetrachlorobiphenyl	4	0	111.8

Table 3 (Continued)

IUPAC no.	compounds	no. of Cl atoms	no. of ortho Cl atoms	CoMFA predicted values
82	2,2',3,3',4-pentachlorobiphenyl	5	2	110.9
83	2,2',3,3',5-pentachlorobiphenyl	5	2	107.7
84	2,2',3,3',6-pentachlorobiphenyl	5	3	101.0
85	2,2',3,4,4'-pentachlorobiphenyl	5	2	111.0
86	2,2',3,4,5-pentachlorobiphenyl	5	2	106.7
87	2,2',3,4,5'-pentachlorobiphenyl	5	2	115.8
88	2,2',3,4,6-pentachlorobiphenyl	5	3	110.4
89	2,2',3,4,6'-pentachlorobiphenyl	5	3	104.9
90	2,2',3,4',5-pentachlorobiphenyl	5	2	113.6
91	2,2',3,4',6-pentachlorobiphenyl	5	3	111.4
92	2,2',3,5,5'-pentachlorobiphenyl	5	2	108.5
93	2,2',3,5,6-pentachlorobiphenyl	5	3	110.2
94	2,2',3,5,6'-pentachlorobiphenyl	5	3	99.7
95	2,2',3,5',6-pentachlorobiphenyl	5	3	100.0
96	2,2',3,6,6'-pentachlorobiphenyl	5	4	98.2
97	2,2',3',4,5-pentachlorobiphenyl	5	2	105.1
98	2,2',3',4,6-pentachlorobiphenyl	5	3	108.1
99	2,2',4,4',5-pentachlorobiphenyl	5	2	107.9
100	2,2',4,4',6-pentachlorobiphenyl	5	3	103.9
102	2,2',4,5,6'-pentachlorobiphenyl	5	3	99.6
103	2,2',4,5',6-pentachlorobiphenyl	5	3	103.6
104	2,2',4,6,6'-pentachlorobiphenyl	5	4	97.8
105	2,3,3',4,4'-pentachlorobiphenyl	5	1	102.2
106	2,3,3',4,5-pentachlorobiphenyl	5	1	100.3
107	2,3,3',4',5-pentachlorobiphenyl	5	1	107.6
108	2,3,3',4,5'-pentachlorobiphenyl	5	1	114.4
109	2,3,3',4,6-pentachlorobiphenyl	5	2	110.8
110	2,3,3',4',6-pentachlorobiphenyl	5	2	113.8
111	2,3,3',5,5'-pentachlorobiphenyl	5	1	112.9
112	2,3,3',5,6-pentachlorobiphenyl	5	2	110.7
113	2,3,3',5',6-pentachlorobiphenyl	5	2	114.8
114	2,3,4,4',5-pentachlorobiphenyl	5	1	102.3
115	2,3,4,4',6-pentachlorobiphenyl	5	2	116.2
116	2,3,4,5,6-pentachlorobiphenyl	5	2	106.6
117	2,3,4',5,6-pentachlorobiphenyl	5	2	115.8
118	2,3',4,4',5-pentachlorobiphenyl	5	1	98.8
119	2,3',4,4',6-pentachlorobiphenyl	5	2	111.9
120	2,3',4,5,5'-pentachlorobiphenyl	5	1	109.8
121	2,3',4,5',6-pentachlorobiphenyl	5	2	112.2
122	2',3,3',4,5-pentachlorobiphenyl	5	1	103.1
123	2',3,4,4',5-pentachlorobiphenyl	5	1	114.2
124	2',3,4,5,5'-pentachlorobiphenyl	5	1	97.3
125	2',3,4,5,6'-pentachlorobiphenyl	5	2	101.8
126	3,3',4,4',5-pentachlorobiphenyl	5	0	106.0
127	3,3',4,5,5'-pentachlorobiphenyl	5	0	105.1
129	2,2',3,3',4,5-hexachlorobiphenyl	6	2	106.2
130	2,2',3,3',4,5'-hexachlorobiphenyl	6	2	114.9
131	2,2',3,3',4,6-hexachlorobiphenyl	6	3	101.8
132	2,2',3,3',4,6'-hexachlorobiphenyl	6	3	103.8
133	2,2',3,3',5,5'-hexachlorobiphenyl	6	2	113.5
134	2,2',3,3',5,6-hexachlorobiphenyl	6	3	106.2
135	2,2',3,3',5,6'-hexachlorobiphenyl	6	3	103.1
136	2,2',3,3',6,6'-hexachlorobiphenyl	6	4	100.8
137	2,2',3,4,4',5-hexachlorobiphenyl	6	2	115.5
138	2,2',3,4,4',5'-hexachlorobiphenyl	6	2	108.1
139	2,2',3,4,4',6-hexachlorobiphenyl	6	3	112.9
140	2,2',3,4,4',6'-hexachlorobiphenyl	6	3	103.0
141	2,2',3,4,5,5'-hexachlorobiphenyl	6	2	111.5
142	2,2',3,4,5,6-hexachlorobiphenyl	6	3	103.7
143	2,2',3,4,5,6'-hexachlorobiphenyl	6	3	102.6
144	2,2',3,4,5',6-hexachlorobiphenyl	6	3	107.8
145	2,2',3,4,6,6'-hexachlorobiphenyl	6	4	100.5
146	2,2',3,4',5,5'-hexachlorobiphenyl	6	2	112.7
147	2,2',3,4',5,6-hexachlorobiphenyl	6	3	115.1
148	2,2',3,4',5,6'-hexachlorobiphenyl	6	3	105.5
149	2,2',3,4',5',6-hexachlorobiphenyl	6	3	106.4
150	2,2',3,4',6,6'-hexachlorobiphenyl	6	4	103.0
151	2,2',3,5,5',6-hexachlorobiphenyl	6	3	109.3
152	2,2',3,5,6,6'-hexachlorobiphenyl	6	4	103.2
153	2,2',4,4',5,5'-hexachlorobiphenyl	6	2	112.9
154	2,2',4,4',5,6'-hexachlorobiphenyl	6	3	105.6
156	2,3,3',4,4',5-hexachlorobiphenyl	6	1	112.7

Table 3 (Continued)

IUPAC no.	compounds	no. of Cl atoms	no. of ortho Cl atoms	CoMFA predicted values
157	2,3,3',4,4',5'-hexachlorobiphenyl	6	1	108.7
158	2,3,3',4,4',6-hexachlorobiphenyl	6	2	119.2
159	2,3,3',4,5,5'-hexachlorobiphenyl	6	1	109.4
160	2,3,3',4,5,6-hexachlorobiphenyl	6	2	120.3
161	2,3,3',4,5',6-hexachlorobiphenyl	6	2	115.0
162	2,3,3',4',5,5'-hexachlorobiphenyl	6	1	111.6
163	2,3,3',4',5,6-hexachlorobiphenyl	6	2	117.7
164	2,3,3',4',5',6-hexachlorobiphenyl	6	2	116.7
165	2,3,3',5,5',6-hexachlorobiphenyl	6	2	118.8
166	2,3,4,4',5,6-hexachlorobiphenyl	6	2	119.7
167	2,3',4,4',5,5'-hexachlorobiphenyl	6	1	104.9
168	2,3',4,4',5',6-hexachlorobiphenyl	6	2	117.0
169	3,3',4,4',5,5'-hexachlorobiphenyl	6	0	114.2
170	2,2',3,3',4,4',5-heptachlorobiphenyl	7	2	113.7
172	2,2',3,3',4,5,5'-heptachlorobiphenyl	7	2	118.7
173	2,2',3,3',4,5,6-heptachlorobiphenyl	7	3	107.3
174	2,2',3,3',4,5,6'-heptachlorobiphenyl	7	3	105.7
175	2,2',3,3',4,5',6-heptachlorobiphenyl	7	3	116.2
176	2,2',3,3',4,6,6'-heptachlorobiphenyl	7	4	103.5
177	2,2',3,3',4',5,6-heptachlorobiphenyl	7	3	109.9
178	2,2',3,3',5,5',6-heptachlorobiphenyl	7	3	110.0
179	2,2',3,3',5,6,6'-heptachlorobiphenyl	7	4	106.0
180	2,2',3,4,4',5,5'-heptachlorobiphenyl	7	2	116.4
181	2,2',3,4,4',5,6-heptachlorobiphenyl	7	3	112.3
182	2,2',3,4,4',5,6'-heptachlorobiphenyl	7	3	108.4
183	2,2',3,4,4',5',6-heptachlorobiphenyl	7	3	113.8
184	2,2',3,4,4',6,6'-heptachlorobiphenyl	7	4	106.1
185	2,2',3,4,5,5',6-heptachlorobiphenyl	7	3	114.0
186	2,2',3,4,5,6,6'-heptachlorobiphenyl	7	4	106.3
187	2,2',3,4',5,5',6-heptachlorobiphenyl	7	3	110.0
188	2,2',3,4',5,6,6'-heptachlorobiphenyl	7	4	109.4
189	2,3,3',4,4',5,5'-heptachlorobiphenyl	7	1	116.2
190	2,3,3',4,4',5,6-heptachlorobiphenyl	7	2	121.2
191	2,3,3',4,4',5',6-heptachlorobiphenyl	7	2	121.4
192	2,3,3',4,5,5',6-heptachlorobiphenyl	7	2	123.0
193	2,3,3',4',5,5',6-heptachlorobiphenyl	7	2	115.6
194	2,2',3,3',4,4',5,5'-octachlorobiphenyl	8	2	135.3
195	2,2',3,3',4,4',5,6-octachlorobiphenyl	8	3	125.0
196	2,2',3,3',4,4',5,6'-octachlorobiphenyl	8	3	115.5
197	2,2',3,3',4,4',6,6'-octachlorobiphenyl	8	4	108.1
198	2,2',3,3',4,5,5',6-octachlorobiphenyl	8	3	116.3
199	2,2',3,3',4,5,5',6'-octachlorobiphenyl	8	3	113.1
200	2,2',3,3',4,5,6,6'-octachlorobiphenyl	8	4	108.7
201	2,2',3,3',4,5',6'-octachlorobiphenyl	8	4	110.7
203	2,2',3,4,4',5,5',6-octachlorobiphenyl	8	3	121.2
204	2,2',3,4,4',5,6,6'-octachlorobiphenyl	8	4	112.2
205	2,3,3',4,4',5,5',6-octachlorobiphenyl	8	2	128.1
206	2,2',3,3',4,4',5,5',6-nonachlorobiphenyl	9	3	122.2
207	2,2',3,3',4,4',5,6,6'-nonachlorobiphenyl	9	4	119.1
208	2,2',3,3',4,5,5',6,6'-nonachlorobiphenyl	9	4	118.3

self-consistency ($r^2 = 0.977$) and internal predictive ability ($r_{cv}^2 = 0.755$).

This model was then used to predict $\Delta_{sub}H_m(298.15\text{ K})$ of the two test-set compounds. The CoMFA-predicted $\Delta_{sub}H_m(298.15\text{ K})$ values were 97.0 kJ/mol (experimental value = 99.5 kJ/mol) for isomer 18 and 103.9 kJ/mol (experimental value = 101.0 kJ/mol) for isomer 52. The differences between experimental and CoMFA-predicted values are small compared to the typical margin of error associated with these measurements.

Upon completion of this external validation process, the two test-set compounds were added to the training set yielding 17 PCBs to construct a final CoMFA model that was used to predict $\Delta_{sub}H_m(298.15\text{ K})$ of the remaining 193 PCB congeners for which experimental values are not available in the literature. Details of this final CoMFA model, generated using *atom fit* alignment and ESP charges, are

given in Table 2. This model exhibited a strong correlation between the corresponding experimental and CoMFA-predicted values (Figure 2).

Although each CoMFA model constructed in this study showed acceptable statistical robustness (i.e., $r^2 > 0.9$, $r_{cv}^2 > 0.5$), the best model was obtained using *atom fit* alignment and ESP charges ($r^2 = 0.976$, $r_{cv}^2 = 0.750$). In light of the high statistical quality of this model, it was used to predict $\Delta_{sub}H_m(298.15\text{ K})$ values for the remaining 193 PCB isomers for which experimental sublimation enthalpies are not available in the literature to the best of our knowledge (Table 3).

The sublimation enthalpy of PCBs depends on the number and position of chlorine atoms on the biphenyl ring, as demonstrated by the CoMFA-predicted values of $\Delta_{sub}H_m(298.15\text{ K})$ in Table 4. Values of sublimation enthalpy increase within a homologous series and tend to increase

Table 4. Averages of the CoMFA-Predicted^a $\Delta_{\text{sub}}H_{\text{m}}(298.15 \text{ K})$ Values^b for the Entire Set of 209 PCBs Grouped According to the Total Number of Chlorine Atoms (Homolog) and the Number of Ortho-Chlorine Atoms

total no. of Cl atoms	average $\Delta_{\text{sub}}H_{\text{m}}(298.15 \text{ K})$				
	0 ^c	1 ^c	2 ^c	3 ^c	4 ^c
2	97.6	97.7	92.8		
3	101.8	95.3	99.7	92.0	
4	103.9	101.5	105.3	96.8	94.8
5	105.6	105.7	110.5	104.8	98.0
6	114.2	109.5	115.6	106.2	102.1
7		116.2	118.6	111.5	106.3
8			131.7	118.2	110.6

^a The CoMFA model (*atom fit* alignment, ESP charges) corresponds to the original data set of 17 PCBs. ^b $\Delta_{\text{sub}}H_{\text{m}}(298.15 \text{ K})$ values in kJ/mol. Note the general trend that the sublimation enthalpies increase as the total number of chlorine atoms increases but decrease as the number of ortho-chlorine atoms increases. ^c Number of ortho-Cl atoms.

for PCBs that are substituted at meta and para positions rather than at the ortho positions. A plausible explanation for this phenomenon is that the crystal-packing arrangements are expected to be more nearly coplanar for meta- and para-substituted compounds, which in turn will give rise to stronger (more attractive) intermolecular interactions. As evidence, the AM1-calculated torsion angle between the phenyl rings is 41° for meta-substituted 3-chlorobiphenyl, yet 60° for ortho-substituted 2-chlorobiphenyl. Correspondingly, the AM1-calculated energy barriers to coplanarity are substantially lower for 3-chlorobiphenyl (8.8 kJ/mol) than for 2-chlorobiphenyl (28.8 kJ/mol).¹⁵

In making these predictions, it should be noted that the experimental values of sublimation enthalpies used to build our CoMFA models are subject to some uncertainty due to differences in experimental techniques and laboratory conditions. Furthermore, it is assumed that the PCBs selected for building these CoMFA models are representative of the entire family of 209 PCB congeners.

CONCLUSIONS

CoMFA has been applied successfully to derive several 3D-QSPR models for the sublimation enthalpies of PCBs at 298.15 K using three different schemes for molecular alignment (*atom fit*, *inertial*, and *as is*) and two different schemes for assigning partial atomic charges (GM, ESP). The combination of *atom fit* and ESP charges yielded the statistically most robust model ($r^2 = 0.976$, $r_{\text{cv}}^2 = 0.750$). This model has been used to predict $\Delta_{\text{sub}}H_{\text{m}}(298.15 \text{ K})$ of PCBs for which experimental values are unavailable. These results encourage the development of CoMFA models for the prediction of thermodynamic properties of other compounds of environmental concern, such as polybrominated diphenyl ethers, polychlorinated dibenzo-p-dioxins, and polychlorinated dibenzofurans.

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