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Enthalpies of sublimation and formation of polycyclic aromatic hydrocarbons (PAHs) derived from comparative molecular field analysis (CoMFA): Application of moment of inertia for molecular alignment

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Abstract

A Quantitative Structure-Property Relationship (QSPR) is developed from the 3D-QSAR method CoMFA to estimate the sublimation enthalpy ($\Delta_{\text{sub}}H_{\text{m}}^0$ (298.15 K)) and formation enthalpy ($\Delta_{\text{f}}H_{\text{m}}^0$ (298.15 K)) of a series of polycyclic aromatic hydrocarbons (PAHs). A unique feature of the present analysis is the application of moment of inertia as the basis for aligning the PAH molecules in the data set, which included nonplanar structures. Partial least-squares (PLS) regression with cross validation was employed to correlate each of the two thermodynamic properties with the steric and electrostatic fields surrounding each PAH molecule. The resulting CoMFA model for $\Delta_{\text{sub}}H_{\text{m}}^0$ (298.15 K) yielded r^2 values of 0.817 (cross-validated) and 0.948 (conventional) using a training set of 30 PAHs, while that for $\Delta_{\text{f}}H_{\text{m}}^0$ (298.15 K) yielded r^2 values of 0.617 (cross-validated) and 0.998 (conventional) using a training set of 16 PAHs. CoMFA-predicted values of $\Delta_{\text{sub}}H_{\text{m}}^0$ (298.15 K) for a test set of 5 PAHs agreed within an average 5% of the corresponding experimental values. Contributions to the CoMFA models from the 3D steric and electrostatic fields were 93% steric and 7% electrostatic for $\Delta_{\text{sub}}H_{\text{m}}^0$ (298.15 K) and 66% steric and 34% electrostatic for $\Delta_{\text{f}}H_{\text{m}}^0$ (298.15 K), reflecting the strong correlation between steric bulk as encoded in the CoMFA steric fields and both of these thermodynamic properties. The present CoMFA models were used to predict the $\Delta_{\text{sub}}H_{\text{m}}^0$ (298.15 K) and $\Delta_{\text{f}}H_{\text{m}}^0$ (298.15 K) values of several PAHs for which the corresponding experimental values are unavailable.

Keywords: Sublimation enthalpy; Formation enthalpy; CoMFA; Moment of inertia; Polycyclic aromatic hydrocarbons (PAHs)

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1. Introduction

Several computational methods have been developed and applied to estimate the normal boiling point [1], vapor pressure [2], and formation enthalpy ($\Delta_{\text{f}}H_{\text{m}}^0$) [3] of organic compounds using either group-additivity approaches or theoretical treatments based on molecular structure. By contrast, relatively few attempts have been made to derive quantitative relationships for sublimation enthalpies ($\Delta_{\text{sub}}H_{\text{m}}^0$) [4]. This is particularly the case for the polycyclic aromatic hydrocarbons (PAHs),

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which have attracted widespread attention in recent years because of the potential adverse health effects on humans associated with exposure to these substances.

Recently, Nass et al. [5] found a general relationship between molecular structure and $\Delta_{sub}H^0_m$ for a set of PAHs containing five- and six-membered rings. They showed that, by taking naphthalene or fluorene as the reference compound, higher homologues could be developed through structural features which contribute a fixed increment to the magnitude of $\Delta_{sub}H^0_m$. In an earlier study, Chickos et al. [6] estimated $\Delta_{sub}H^0_m$ (298.15 K) for a series of solid hydrocarbons using a method described as Semiempirical Additivity of Latent Enthalpies (SEALE). In their model, vaporization enthalpies ($\Delta_{vap}H^0_m$) of liquid hydrocarbons were first calculated from a two-parameter equation which includes the number of quaternary carbon atoms and, together with available fusion enthalpies, reasonable estimates of $\Delta_{sub}H^0_m$ (298.15 K) were obtained based on the additivity of latent enthalpies [7].

Since its conception in 1988 by Cramer et al. [8], the Comparative Molecular Field Analysis (CoMFA) method of three-dimensional quantitative structure-activity relationships (3D-QSAR) has established itself as a versatile and powerful tool in rational drug design and related applications [9]. CoMFA is based on the assumption that most drug-receptor interactions are both noncovalent in nature and shape-dependent, hence a 3D-QSAR can be derived by sampling the steric and electrostatic fields surrounding a set of molecules and correlating the changes in those fields to changes in the biological activities or binding affinities. The multivariate regression technique of partial least-squares (PLS) is then employed to derive a QSAR from the large CoMFA data table so produced. More recently, the CoMFA method has been extended successfully to predict classical QSAR descriptors such as the logarithm of the octanol/water partition coefficient [10], the Hammett constant τ [11], and the LUMO energy [12].

In a recent CoMFA study in this Laboratory, Collantes et al. [13] identified a strong correlation between the liquid chromatographic (LC) retention index and the CoMFA-derived stereoelectrostatic properties for a set of PAHs. Since LC retention and sublimation enthalpy are both thermophysical properties which depend on the strength of intermolecular interactions, we postulated that a CoMFA model similar to that derived for the LC study on these PAHs should be suitable for modeling the $\Delta_{sub}H^0_m$ (298.15 K) values for a comparable data set. The CoMFA approach appeared to be particularly well-suited for modeling sublimation enthalpies since the strength of intermolecular interactions are implicitly encoded in the 3D steric and electrostatic fields generated by CoMFA. Hence, the present study was motivated by our desire to derive a 3D Quantitative Structure-Property Relationship (3D-QSPR) which correlates $\Delta_{sub}H^0_m$ (298.15 K) values with the CoMFA-generated stereoelectrostatic fields surrounding the PAH molecules. Conveniently, 17 of the PAHs in our original CoMFA study of LC retention [13] were also contained in the data set of PAHs for which Nass et al. reported $\Delta_{sub}H^0_m$ values [5]. However, a distinction between the two data sets was the latter's inclusion of some nonplanar and substituted structures (e.g., biphenyl and 9,10-diphenylanthracene) besides the all-planar fused-ring PAH structures. Hence, the present study was also motivated by our desire to evaluate the utility of the moment of inertia I as the basis for aligning a structurally more diverse set of PAHs including nonplanar molecules.

While concluding the CoMFA analysis of $\Delta_{sub}H^0_m$ (298.15 K), we discovered a recently published data set [14] of experimental formation enthalpies $\Delta_f H^0_m$ which contained many of the same 6-membered PAHs present in our $\Delta_{sub}H^0_m$ (298.15 K) data set. The availability of $\Delta_f H^0_m$ values for these PAHs presented a convenient opportunity to construct and evaluate the appropriate CoMFA models for $\Delta_f H^0_m$ in addition to $\Delta_{sub}H^0_m$ (298.15 K). Therefore, results from this separate analysis of formation enthalpies are included.

2. Methodology

2.1. PAH Data Set

The list of 30 PAHs in the data set of Nass et al. [5] was taken as the training set. For 26 of these

PAHs, experimental $\Delta_{\mathrm{sub}}H_{\mathrm{m}}^{0}$ values were obtained from several published compilations [4,15]. Values reported at 298 K, whenever available, were chosen for the analysis. For experimental $\Delta_{\mathrm{sub}}H_{\mathrm{m}}^{0}$ values reported at temperatures other than 298 K, adjustments to 298 K were carried out following the procedure for heat capacity correction as described by Chickos et al. [16]. In the absence of other experimental values for the remaining 4 of the 30 PAHs in the data set, those reported by Nass et al. [5] were chosen after appropriate temperature adjustment to 298 K. The procedure applied for this purpose requires some comment. Specifically, Nass et al. measured the vapor pressure P in the temperature range 40–180°C (i.e., ~ 313–453 K). Assuming validity of the Clausius-Clapeyron equation, they then derived sublimation enthalpies at some intermediate temperature from the slope of the ln P versus $1/T$ straight line. Given the reciprocal nature of the ln P versus T relationship, it was judged more appropriate for the present study to estimate this intermediate temperature over the 313–453 K range from the mean of $1/T$ (i.e., 370 K) rather than from the mean of T (383 K). Accordingly, the sublimation enthalpies reported by Nass et al. for these 4 PAHs were adjusted from 370 K to 298 K using again the method of Chickos et al. [16].

It should be noted that experimental values of the sublimation enthalpy and formation enthalpy were chosen to be internally consistent in the sense that they should differ by the value of $\Delta_{\mathrm{f}}H_{\mathrm{m}}^{0}$. (crystal) in each case. To ensure consistency, the experimental values of $\Delta_{\mathrm{sub}}H_{\mathrm{m}}^{0}$ (298.15 K) and $\Delta_{\mathrm{f}}H_{\mathrm{m}}^{0}$ (298.15 K) listed in Table 1 were checked for agreement with the self-consistent compilation of values given in Pedley et al. [17]. This step was important inasmuch as such inconsistencies can easily arise when one considers the large range of experimental values for thermodynamic properties (i.e., sublimation enthalpy) reported for some compounds.

2.2. *Molecular modeling*

All molecular modeling and CoMFA computations described herein were performed on Silicon Graphics Indigo and Indy workstations using the SYBYL 6.1 molecular modeling software [18] from Tripos, Inc, St. Louis, MO. Of the 30 PAH structures in the data set, 17 were taken from our previous CoMFA study [13]. The remaining structures were generated using the BUILD option then geometry optimized to a convergence criterion of 0.001 kcal mol^{-1} (0.004184 kJ mol^{-1}) energy gradient using the standard Tripos molecular mechanics force field with a distance-dependent dielectric function to scale the electrostatic term. Partial atomic charges were computed using the Gasteiger-Marsili method [19].

2.3. *CoMFA alignment and analysis*

In practice, a CoMFA analysis typically begins by structurally aligning all molecules belonging to the training set within a fixed 3D lattice. A crucial aspect of every CoMFA study is the specific paradigm, known as the alignment rule, applied for this molecular superposition. Following our earlier CoMFA study [13], the PAHs were aligned by superimposing the principal moments of inertia I. According to this scheme, the 'pharmacophore' constitutes the entire PAH molecule rather than selected portions deemed essential for activity. This ensures that the effect of every atom in the molecule is factored into the alignment and fitting procedure.

The two moments of inertia I_x and I_y, for benzo[b]fluoranthene are depicted in Fig. 1. The moment of inertia I of a molecule about a particular axis is expressed as $I = \Sigma m_i r_i^2$, where m_i is the atom's mass and r_i is its perpendicular distance to that axis. The Cartesian coordinate system for each molecule was thus transformed to the principal moments of inertia I_x, I_y, and I_z such that the origin of the three principal axes is located at the center of mass of the molecule under consideration. The x-axis is then defined as coinciding with the smallest moment of the molecule; the y-axis is defined as coinciding with the smallest moment which is orthogonal to the x-axis, and the z-axis is drawn normal to the xy plane. Moreover, the moments on the positive side of each of the axes are equal to or greater than the moments on their respective negative side. This is particularly significant in cases of asymmetric molecules such as 4,5-dimethylphenanthrene or nonplanar molecules such as biphenyl. Orientation of the I as described assures a maximum overlap of the steric molecular fields of the PAHs and resolves the

Table 1

Comparison of Experimental and CoMFA-calculated Values of the Sublimation Enthalpy ($\Delta_{sub}H^0_m$ (298.15 K)) and Formation Enthalpy ($\Delta_f H^0_m$ (298.15 K)) for the PAHs in the training set. The residual is the difference between experimental and calculated value

Formula	PAH compound	$\Delta_{sub}H^0_m$ (298.15 K) (kJ mol^{-1})			$\Delta_f H^0_m$ (298.15 K) (kJ mol^{-1})		
		exptl.[a,b]	calcd.	residual	exptl.[k,l]	calcd.	residual
$C_{10}H_8$	Naphthalene	72.3	75.0	−2.7	150.6	158.4	−7.8
$C_{12}H_8$	Acenaphthylene	73.0	76.1	−3.1		(176.9)[m]	
$C_{12}H_8$	Biphenylene	87.3	81.9	5.4		(191.9)	
$C_{12}H_{10}$	Acenaphthene	83.4	76.9	6.5	155.0[f]	154.0	1.0
$C_{12}H_{10}$	Biphenyl	81.5	90.3	−8.8	181.1[f]	180.2	0.9
$C_{13}H_{10}$	Fluorene	85.1[c]	84.7	0.4		(167.0)	
$C_{14}H_{10}$	Anthracene	104.5	99.1	5.4	230.9	226.4	4.5
$C_{14}H_{10}$	Phenanthrene	90.9	93.2	−2.3	207.9	207.0	0.9
$C_{14}H_{12}$	Dihydroanthracene	93.9	98.0	−4.1	159.7[f]	160.6	−0.8
$C_{16}H_{10}$	Fluoranthene	99.2	101.3	−2.1	289.0[f]	284.7	4.3
$C_{16}H_{10}$	Pyrene	100.2[d]	99.5	0.7	225.9	225.8	0.1
$C_{16}H_{12}$	1-Phenylnaphthalene	91.3[e]	87.3	4.0		(362.5)	
$C_{16}H_{14}$	4,5-Dimethylphenanthrene	104.6[f]	102.1	2.5	193.6[f]	191.4	2.2
$C_{17}H_{12}$	Benzo[a]fluorene	107.9[e]	113.9	−6.0		(258.5)	
$C_{17}H_{12}$	Benzo[b]fluorene	113.7[e]	119.1	−5.4		(263.8)	
$C_{18}H_{12}$	Benzanthracene	123.3[g]	120.6	2.7	294.1	303.8	−9.7
$C_{18}H_{12}$	Benzo[c]phenanthrene	106.3[g]	115.1	−8.8	291.2	292.4	−1.2
$C_{18}H_{12}$	Chrysene	131.4	128.2	3.2	276.1	275.6	0.5
$C_{18}H_{12}$	Naphthacene	143.7	135.2	8.5	302.5	297.0	5.5
$C_{18}H_{12}$	Triphenylene	126.5	121.8	4.7	278.2	276.1	2.1
$C_{20}H_{12}$	Benzo[b]fluoranthene	122.2[e]	128.1	−5.9		(305.8)	
$C_{20}H_{12}$	Benzo[a]pyrene	121.4[h]	129.7	−8.3		(314.9)	
$C_{20}H_{12}$	Benzo[e]pyrene	122.2[h]	126.6	−4.4		(335.3)	
$C_{20}H_{12}$	Perylene	145.2[i]	130.2	15.0	328.0	33.0	−2.0
$C_{20}H_{14}$	9-Phenylanthracene	118.6	113.8	4.8		(414.3)	
$C_{22}H_{12}$	Benzo[g,h,i]perylene	132.3[h]	135.2	−2.9		(346.8)	
$C_{22}H_{14}$	Dibenz[a,c]anthracene	159.0	154.2	4.8		(357.2)	
$C_{22}H_{14}$	Dibenz[a,h]anthracene	162.0	160.1	1.9		(363.5)	
$C_{24}H_{12}$	Coronene	142.2[h]	139.9	2.3		(352.8)	
$C_{26}H_{18}$	9,10-Diphenylanthracene	156.9[j]	164.9	−8.0	465.6[f]	466.0	−0.4

[a] Temperature correction to 298.15 K, where applicable, was done following Ref. [16].

[b] Ref. [4c] unless noted otherwise.

[c] Ref. [15c].

[d] Ref. [15b]

[e] Ref. [5].

[f] Ref. [17].

[g] Ref. [4a].

[h] Ref. [15a].

[i] Ref. [15d].

[j] Ref. [15e].

[k] $\Delta_f H^0_m$ (298.15 K) refers to the gaseous state.

[l] Ref. [14] unless noted otherwise.

[m] Parentheses denote values predicted by CoMFA for which no experimental data were available.

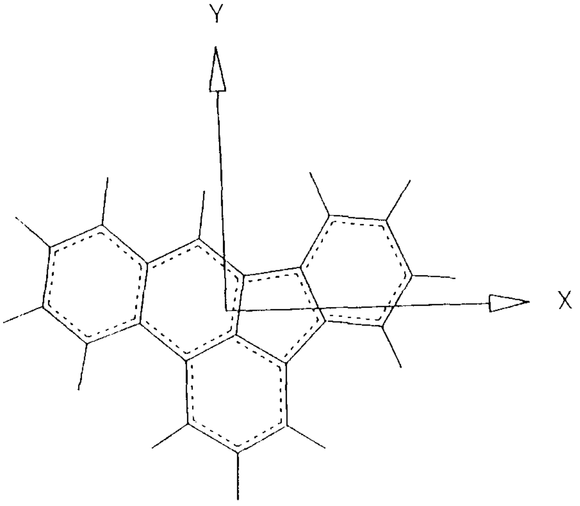

Fig. 1. The moment of inertia (*I*) for benzo[b]fluoranthene is illustrated. The molecular plane coincides with the *x*, *y* plane. All PAHs in the training set were aligned based on *I*. The *x* and *y* axes are defined as described in the Methodology under *CoMFA alignment and analysis*.

arbitrary nature of alignment associated with these compounds.

Following energy minimization, the PAH structures in the data set were aligned by superimposing each PAH molecule along its three coordinate axes corresponding to the principal moments of inertia. After alignment of the molecules in this manner, each PAH molecule was placed in the center of a regularly-spaced 3D grid of 2.0 Å units in all *x*, *y*, and *z* directions. Electrostatic (Coulombic) and steric (Lennard-Jones) potential energies were then calculated at each lattice intersection between the PAH molecule and a probe consisting of an sp^3-hybridized carbon atom with a +1 charge. This probe was specifically chosen to capture the steric effects experienced by a PAH molecule in a hydrophobic environment such as that existing in a crystalline lattice of nonpolar PAH molecules. A distance-dependent dielectric function was applied, and the steric and electrostatic interaction energies were truncated at 30 kcal mol^{-1} (125 kJ mol^{-1}).

2.4. PLS-QSPR

Partial least-squares (PLS) [20] is a regression technique for establishing a relationship between *Y* and *X*, where vector *Y* is the response or dependent variable (e.g., the target thermodynamic property) and *X* represents the descriptor data (e.g., the CoMFA interaction energies). All calculations were carried out with the SYBYL QSAR module. The training sets contained 30 PAHs for $\Delta_{\mathrm{sub}}H^0_{\mathrm{m}}$ (298.15 K) and 16 PAHs for $\Delta_{\mathrm{f}}H^0_{\mathrm{m}}$ (298.15 K). Each QSAR table was constructed with rows containing the PAHs along with their appropriate $\Delta_{\mathrm{sub}}H^0_{\mathrm{m}}$ (298.15 K) [5,15] or $\Delta_{\mathrm{f}}H^0_{\mathrm{m}}$ (298.15 K) [14,17] values representing the dependent variables and with columns containing the steric and electrostatic fields calculated as described above representing the independent variables.

An initial PLS analysis was performed using the "leave-one-out" cross validation procedure [21] to determine the optimum number of principal components, which are linear combinations of the original variables, needed for the subsequent analysis of the data. In cross validation, each compound is systematically excluded from the data set and its activity or property predicted by a model that is derived from the remaining compounds. The PLS analysis was then repeated without cross validation using the optimum number of components corresponding to that which yielded the smallest standard error of prediction or the highest cross-validated r^2 value. This final analysis yielded a predictive model and associated conventional r^2 values, from which the CoMFA coefficient contour plots for the steric and electrostatic potentials could be generated.

A test set of 5 PAHs, not included in the training set, was used to evaluate the predictive power of the CoMFA model so derived in estimating $\Delta_{\mathrm{sub}}H^0_{\mathrm{m}}$ (298.15 K). Three of these test set compounds were from our original CoMFA study on the PAHs [13] for which experimental $\Delta_{\mathrm{sub}}H^0_{\mathrm{m}}$ values were available [15] and which were corrected to 298 K [16].

3. Results and discussion

3.1. CoMFA model of the PAHs for sublimation enthalpies

Results from the CoMFA study on the training set of $\Delta_{\mathrm{sub}}H^0_{\mathrm{m}}$ (298.15 K) values for 30 PAHs are

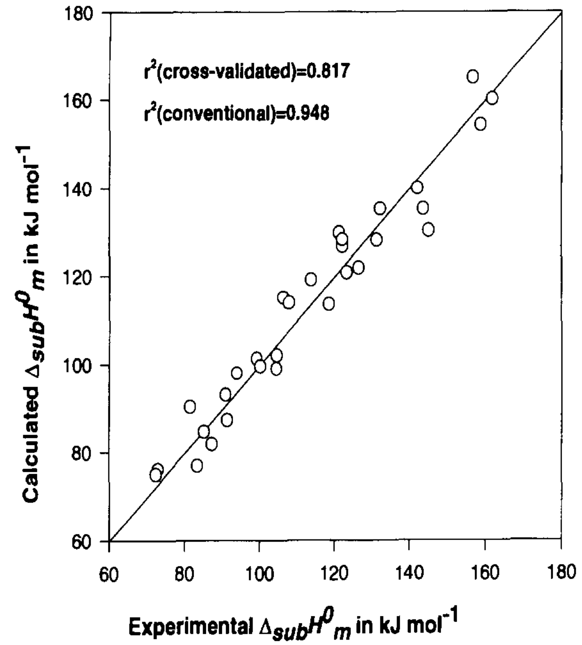

Fig. 2. Calculated versus experimental sublimation enthalpies $\Delta_{sub}H^0_m$ (298.15 K) for 30 PAHs in the training set.

summarized in Table 1. The model required 3 principal components to explain the variance in $\Delta_{sub}H^0_m$ (298.15 K). The r^2 values were 0.817 (cross-validated) and 0.948 (conventional), with a standard error of estimate of 6.139 kJ mol^{-1}. The cross-validated $r^2 = 0.817$ is well above the threshold value of 0.5 which specifies that the model is predictive [21]. The high level of statistical significance indicates that the PAHs in the data set are strongly correlated to each other and, moreover, that this model is useful for predicting sublimation enthalpies for PAHs outside of the training set. The excellent linearity between the CoMFA-calculated and experimental $\Delta_{sub}H^0_m$ (298.15 K) values (data in Table 1) is illustrated in Fig. 2. The deviations between the CoMFA-calculated and experimental $\Delta_{sub}H^0_m$ (298.15 K) values ranged from 1%, as for fluorene and pyrene, to ca. 10%, as for biphenyl and perylene. These deviations are small compared with the typical error associated with these measurements [7].

The CoMFA model for the sublimation enthalpies of these PAHs consists of 93% contribution from the steric fields and 7% contribution from the electrostatic fields, thus indicating that the differences in the $\Delta_{sub}H^0_m$ (298.15 K) values can be ascribed almost totally to the steric fields with negligible influence by the electrostatic fields. This finding is consistent with the physical nature of sublimation enthalpy, which should increase within a series of nonpolar compounds as the intermolecular steric (i.e., London dispersion) attractions increase as a function of molecular size. It is also consistent with the correlation observed between surface area and vaporization enthalpy [22].

An attractive feature of CoMFA is its ability to visualize the steric and electrostatic fields as 3D contour maps which represent regions where increased steric bulk, as well as positive or negative charge, diminishes or enhances the value of the target property (e.g., $\Delta_{sub}H^0_m$ (298.15 K)). The composite 3D contour map of the CoMFA steric field for the entire training set of PAHs is depicted in Fig. 3. Anthracene, a representative training-set PAH, is shown placed in its properly aligned orientation within the steric field for easy viewing of the relative molecule-field positions. This steric contour plot shows a band of polyhedra encompassing the periphery of the molecule, where the contours depict regions where adding steric bulk to the PAH molecule correlates with an increase in sublimation enthalpy. Thus, CoMFA found that increasing the number of rings as well as substituting at any of the ring positions led to increases in $\Delta_{sub}H^0_m$ (298.15 K) values for this data set. Overall, the extensive amount of space occupied by the steric contours highlights the primacy of steric (dispersion) interactions in quantifying differences in $\Delta_{sub}H^0_m$ (298.15 K) values among these PAHs.

3.2. *Validation of CoMFA model for sublimation enthalpies*

Comparison of the corresponding CoMFA-predicted and literature [15] $\Delta_{sub}H^0_m$ (298.15 K) values for the 5 PAHs in the test set reveal an average deviation of only 5% (Table 2). In the case of 7,12-dimethylbenzanthracene, experimental values of 139.3 kJ mol^{-1} and 112.0 kJ mol^{-1} (after correction to 298 K) were extracted from the literature [15a]. To choose between these two disparate values, we compared these values with that obtained (i.e., 140

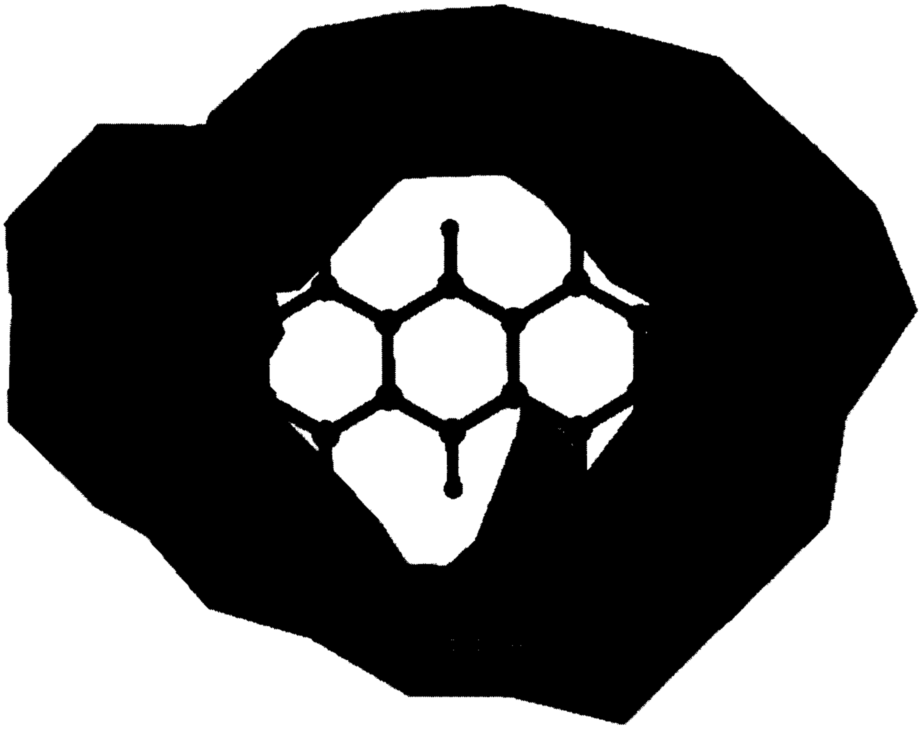

Fig. 3. Plot of the composite CoMFA STDEV*COEFF steric contour for the entire training set of PAHs. Anthracene, a representative PAH, is shown placed in its properly aligned position inside the field. The contours depict regions where increased steric bulk contributes to a larger $\Delta_{\mathrm{sub}}H^0_{\mathrm{m}}$ (298.15 K) value. The x-axis coincides with the long molecular axis, while the y-axis is normal to the x-axis and in the molecular plane.

kJ $\mathrm{mol^{-1}}$) by summing the experimental vaporization enthalpy [15a] with the fusion enthalpy estimated by a group-additivity method [23]. Based on this comparison, the former value (i.e., 139.3 kJ $\mathrm{mol^{-1}}$) appears to be closer to the correct experimental value. Consistent with this experimental value, CoMFA predicted a value of 132.6 kJ $\mathrm{mol^{-1}}$ (Table 2).

3.3. *CoMFA model of the PAHs for formation enthalpies*

Results of the CoMFA study on the training set of $\Delta_{\mathrm{f}}H^0_{\mathrm{m}}$ (298.15 K) values for 16 PAHs are given in Table 1. The model required 6 principal components to explain the variance in $\Delta_{\mathrm{f}}H^0_{\mathrm{m}}$ (298.15 K), yielding r^2 values of 0.617 (cross-validated) and 0.998 (conventional) with a standard error of estimate of 5.18 kJ $\mathrm{mol^{-1}}$. A plot of the CoMFA-calculated versus experimental $\Delta_{\mathrm{f}}H^0_{\mathrm{m}}$ (298.15 K) values (Fig. 4) confirms the strong linear correlation. Unlike the situation for the sublimation enthalpies where the field contributions to the model were 93% steric and 7% electrostatic, those for the formation enthalpies are 66% steric and 34% electrostatic. The contribution of the steric fields is still dominant in explaining the variation in $\Delta_{\mathrm{f}}H^0_{\mathrm{m}}$ (298.15 K) values among these PAHs; nevertheless, the significant contribution of the electrostatic fields is noteworthy.

It may at first seem counterintuitive that CoMFA would serve as an appropriate modeling scheme for a thermodynamic property such as formation enthalpy. After all, the steric and electrostatic fields generated by CoMFA are formulated to model intermolecular (e.g., drug-receptor) nonbonded in-

Table 2
Comparison of Experimental and CoMFA-predicted Values of the Sublimation Enthalpy ($\Delta_{sub}H^0_m$ (298.15 K)) for PAHs in the test set. The residual is the difference between the experimental and predicted value.

Formula	PAH compound	$\Delta_{sub}H^0_m$ (298.15 K) (kJ mol^{-1})		
		exptl.[a,b]	predicted	residual
$C_{20}H_{12}$	Benzo[k]fluoranthene	133.3[c]	141.4	−8.1
$C_{20}H_{16}$	5,6-Dimethylchrysene	138.7	132.3	6.4
$C_{20}H_{16}$	7,12-Dimethylbenzanthracene	139.3[c]	132.6	6.7
$C_{22}H_{12}$	Anthanthrene	142.7	139.3	3.4
$C_{22}H_{14}$	Picene	146.7	157.2	−10.5

[a] Temperature correction to 298.15 K was made for all compounds following Ref. [16].
[b] Ref. [4c].
[c] Ref. [15a].

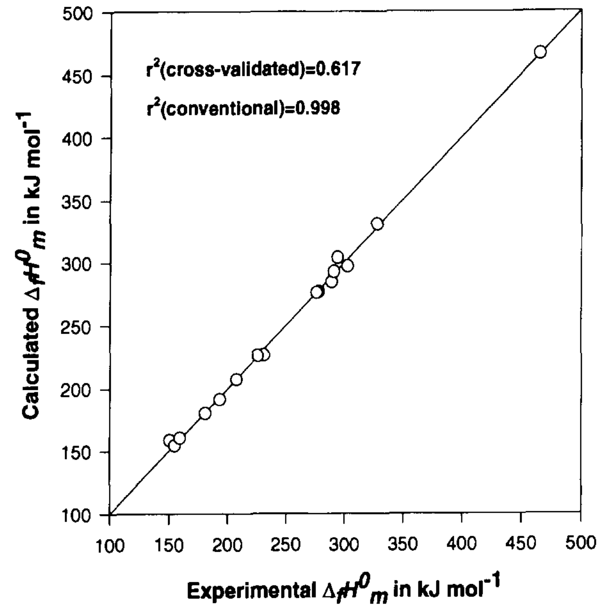

Fig. 4. Calculated versus experimental formation enthalpies $\Delta_fH^0_m$ (298.15 K) for 16 PAHs in the training set.

teractions rather than intramolecular bonding interactions such as those resulting from the formation of covalent bonds within a PAH molecule. Just the same, the present results found a strong linear correlation between the CoMFA fields and the $\Delta_fH^0_m$ (298.15 K) values. A rationale for this behavior can be understood by considering that CoMFA encodes implicitly for steric bulk in its steric fields. Likewise, the $\Delta_fH^0_m$ (298.15 K) values for this series of PAHs should correlate with steric bulk in relation to the number of covalent bonds in the structure. As the number of rings in the structure increases, so too will both the steric bulk (encoded by CoMFA) and the $\Delta_fH^0_m$ (298.15 K) value. The PAHs in this data set all possess six-membered rings, hence the $\Delta_fH^0_m$ (298.15 K) values and steric bulk are simple functions of the number of rings in the structure. For example, the $\Delta_fH^0_m$ (298.15 K) values are lowest for naphthalene (2 rings), moderate for pyrene (4 rings), and high for perylene (5 rings) (Table 1). This observation is consistent with the analysis of Cash [3] who reported that the number of rings in polyhex PAHs is a useful predictor of $\Delta_fH^0_m$ (298.15 K) values.

The CoMFA models derived herein can be extremely useful for predicting the thermodynamic properties of those PAHs for which the corresponding experimental values are either unavailable or unreliable. Among the PAHs listed in Table 1, fourteen compounds have experimental values of $\Delta_{sub}H^0_m$ (298.15 K) but not $\Delta_fH^0_m$ (298.15K). The CoMFA-predicted values for these fifteen missing quantities are denoted in parentheses in Table 1. It is hoped that publication of these predicted values of the thermodynamic properties will serve to encourage experimental investigations of these compounds.

A measure of the predictive power of the CoMFA model for $\Delta_fH^0_m$ (298.15K) can be gained by comparing it with the results from an independent theoretical approach. Table 1 contains ten PAHs for which Herndon et al. [14] calculated the formation enthalpy by molecular mechanics (MM) in addition to providing experimental values. The availability of both MM- and CoMFA-calculated values, together with the corresponding experimental values, for these ten PAHs (see footnote 1 in Table 1) presented an opportunity for direct comparison of the MM- and CoMFA-calculated values against the experimental values. The root mean-square deviation (rmsd) between the calculated and experimental values was 9.56 kJ mol^{-1} for the MM treatment and 4.65 kJ mol^{-1} for the present CoMFA model. It should be noted that CoMFA represents a separate independent method for estimating the sublimation enthalpies and formation enthalpies of the subject PAHs and is not intended nor regarded as a substitute for MM (or any other theoretical approach). Nevertheless, CoMFA and similar 3D-QSAR approaches can prove themselves invaluable in cases where the required experimental value is either unavailable or unreliable or in cases where one must choose among widely dissimilar experimental values derived from different sources and protocols.

As a final word of precaution, it should be remembered that many members of the PAH family of compounds were omitted in the present study and that, strictly speaking, the CoMFA models developed here apply only to the subset of PAHs contained in the training set. Furthermore, it must be assumed that the experimental values of sublimation enthalpy and formation enthalpy selected for developing the present CoMFA models are subject to some uncertainty due to differences in experimental techniques, laboratory conditions, and modes of implementation. In fact, these differences can give rise to appreciable discrepancies.

4. Conclusions

The results of the present study demonstrate the utility of CoMFA as an alternative computational tool for modeling and even predicting the $\Delta_{sub}H^0_m$ (298.15 K) and $\Delta_f H^0_m$ (298.15 K) values for the subject PAHs. In addition, the results extend the application of the moment of inertia in the alignment rule for QSPR studies to data sets which include nonplanar structures. This moment-of-inertia alignment paradigm in CoMFA is currently being extended beyond the PAHs to other classes of compounds of environmental concern, most notably the polychlorinated biphenyls (PCBs) [24] whose polarity renders them structurally distinct from the PAHs.

The CoMFA models derived herein reveal that the steric fields dominate relative to the electrostatic fields in terms of explaining variations in both the sublimation enthalpy and formation enthalpy. The contributions from the steric fields are 93% in the case of sublimation enthalpy, reflecting the primacy of intermolecular steric (dispersion) forces and surface area in accounting for the sublimation properties of these PAHs. The excellent predictive ability of the CoMFA models, as indicated by the cross-validated r^2 values of 0.817 for $\Delta_{sub}H^0_m$ (298.15 K) and 0.617 for $\Delta_f H^0_m$ (298.15 K), confirms the suitability of this 3D-QSPR approach for estimating these thermodynamic properties of PAHs.

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