A QSAR Model of PAHs Carcinogenesis Based on Thermodynamic Stabilities of Biactive Sites

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Polycyclic aromatic hydrocarbons (PAHs) have been adopted to study the carcinogenesis of chemicals experimentally and theoretically. A model of carcinogenic activity of 48 PAHs was obtained based on the calculated relative thermodynamic stabilities of epoxide and carbonium intermediates of the PAHs. Using both epoxyl-energy and cationized-energy of two active sites, the model reasonably predicts the carcinogenic activity of these PAHs and shows a good ability to distinguish between carcinogenic and noncarcinogenic PAHs. Furthermore, the model suggests that double active sites and their distance characteristics are important factors in the chemical carcinogenesis of PAHs. The physical meaning of the energies corresponding addition reactions with DNA is also discussed.

INTRODUCTION

Polycyclic aromatic hydrocarbons (PAHs) are a group of environmental pollutants, which are products of incomplete combustion of fossil fuels. Most PAHs are mutagenic in cell experiments and carcinogenic to animals and humans.[1,2] Because of their distinct structural characteristics, biophysical properties and potent carcinogenicity, they have been frequently adopted to study chemical carcinogenesis and carcinogenic mechanisms. It is believed that most PAHs are natively inactive and need to be metabolized to active metabolites by P450 enzymes. The epoxides of carcinogenic PAHs are more potent than the parent PAHs and can be further metabolized to *trans*-dihydrodiol-epoxides by microsomal epoxide hydrolase, which are called ultimate carcinogens.[3]

In most cases, Bay region adducts were found to be the main addition products with DNA. For example, the Bay region adducts of the benzo[*a*]pyrene, 7,8,9,10-tetrahydro-7,8,9-trihydroxylbenzo[*a*]pyren-10-adducts, are the most common products identified in the experiments.[4,5] They show that the corner ring in the Bay region is easily oxidized by the P450. Although Bay-region diol-epoxides are believed to be the ultimate metabolic carcinogens for several classes of PAHs, increasing evidence shows that other region adducts can also be formed and that these adducts are important to PAH carcinogenesis too. One type of these adducts are the K-region adducts[6] which were found in some experiments[7−9] and are assumed to contribute to the carcinogenicity or mutagenicity of these PAHs. In addition to the epoxidation approach, single electron oxidization is another approach to form PAH-DNA adducts.

Theoretical models have also been developed to explore the genetic toxicity of PAHs. Several QSAR models of PAHs were suggested by CoMFA calculations.[10−12] Welsh related PAHs' unique structural characteristics to their physicochemical and biochemical properties.[13] The photoinduced toxicity of PAHs has been studied using physical and empirical models.[14] Veith's QSAR model indicated that the HOMO−LUMO gap can be used to distinguish phototoxic chemicals from nonphototoxic chemicals.[15] Electron density shape features,[16] molecular polarizability, molecular weight, heat of formation,[17,18] molecular quantum similarity,[1] retention index, and other physical or structural properties[18−20] have also been used as descriptors in different QSAR models of PAHs. More information can be found in Sabljic's review.[21]

Based on his calculation, Dai proposed that the development of two reactive centers on a carcinogenic compound are critical in carcinogenesis, and the most favorable distance between the two centers for carcinogenic potential is 2.8−3.0 Å.[22,23] Our studies on the reactivity and cross-link structures of metabolites of butadiene, acrolein derivatives, and α-dicarbonyl compounds with nucleosides[24−26] demonstrates that these agents can form cross-linking products with DNA and that the cross-linked DNA duplexes deform little and retain native structures. The reacting activities of these agents with nucleosides have a good correlation to their genetic toxicity. Similar cross-linking products have been identified experimentally.[27]

In this work, we have used a semiempirical method (AM1) to calculate the relative thermodynamic stabilities of the epoxide and ring-opening carbonium ion intermediates of 48 PAHs and to establish a QSAR model of the carcinogenesis of PAHs to explore carcinogenic mechanisms of PAHs.

METHODS

All molecules were built and analyzed using the Alchemy program (Tripos Inc.). The AM1 semiempirical Hamiltonian in the MOPAC7 package was used in calculations. Full

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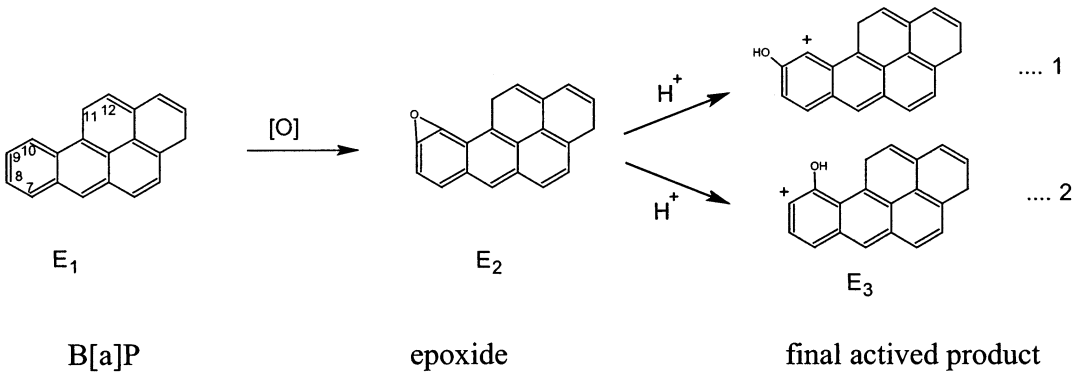


Figure 1. The reaction scheme for benzo[*a*]pyrene.

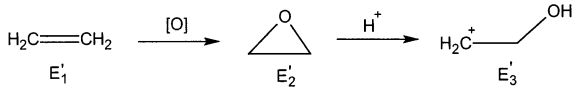


Figure 2. The equivalent net reaction of ethylene.

geometric optimization was performed on each molecule. Heats of formation were obtained through the calculations. All data analysis and regressions were performed using Statistica (StatSoft Inc.) and MOE (Chemical Computing Group) software.

Energy Calculation. As stated above, a PAH can be activated to form epoxides and diol-epoxides, and then the metabolites can form adducts with DNA under in vivo conditions. We used the following simplified approach to simulate the process. For example, benzo[*a*]pyrene (B[a]P) can be oxidized to an B[a]P-epoxide and then protonated to a B[a]P-carbonium ion. As shown in Figure 1, when an epoxide ring forms on C^9 and C^{10} of B[a]P, it can be opened on either C^9 or C.[10] We calculated the energies of the parent B[a]P (E_1), the epoxide (E_2), and the two proposed carbonium ions (E_3) on every possible peripheral bonds of B[a]P. All other PAHs were calculated in the same way.

During the process, an oxygen atom and a proton are introduced into the system and some bonds are changed. To remove the contribution of these changes from the total energy changes and just focus on the energy changes due to the delocalization of π orbital system, the analogous energy change in the similar process of ethylene (Figure 2) is subtracted from the calculated energy change of PAHs.

The relative energy changes ΔE_1 (we call it "epoxyl-energy") and ΔE_2 ("cationized-energy") were calculated using the following equations:

$$\Delta E_1 = (E_2 - E_1) - (E_2' - E_1') \quad (1)$$

$$\Delta E_2 = (E_3 - E_2) - (E_3' - E_2') \quad (2)$$

These energy changes mainly reflect the effects of the delocalization of π orbitals on the reactions. The energy difference between the two carbonium ions, ΔE_0 (the energy difference between (1) and (2) in Figure 1), was also calculated.

Active Sites Selection. If ΔE_0 of a region is significant (≥ 0.05 eV·mol^{-1}), we treat the region as an active region. Because the Bay-region ring (C7−C8−C9−C10 ring on B[a]P) of a carcinogenic PAH tends to be activated easily and to react with DNA in most cases, it is treated as the most likely active region on the PAH. The carbonium ion with the lowest energy is treated as the most probable activated intermediate. The carbonium position, which indicates the potential position reacting with DNA, is treated as the first active site. If there is no active Bay-region, then an active K-region is taken as the first active site.

The following rules are used to select the second active site. If the molecule has an active K-region, the active K-region is treated as the second active site. Otherwise another active Bay-region, if it exists, is treated as the second active site. At the same time, we introduce a structural restraint into the selection of the second active site. If an active site is more than six C−C bonds away from the first active site, we do not treat it as the second active site. If there is no second active site, we assume small empirical values to enable multiple statistic and regression analysis.

Normally, the carcinogenic activities of PAHs are obtained from animal experiments or long time surveys. The carcinogenic activity of a PAH varies with different animals, and even with the same animal, it varies in different routes of exposure (e.g., oral and skin). Even using the same routes of exposure on the same animal, it is normally hard to quantitatively compare the activities from different experiments. Thus, it is hard or impractical to quantify the carcinogenic activity of PAHs. We use a common five-level index system (++++, +++, ++, +, −) to denote the activity of PAHs in this work.

RESULTS AND DISCUSSION

The calculated energies of the first and second active sites are listed in Table 1.

A Factor and Principal component analysis was performed on these calculated energy terms against the carcinogenic activity of the PAHs. In the analysis, we tried to use energy terms that are meaningful in the reactions of PAH metabolism and reactions with DNA. The variables that have a high correlation with activity of PAHs were analyzed, and the results are listed in Table 2. From these results, we can see that $\Delta E_{0,f}$ and $\Delta E_{0,s}$ (where f and s denote the first and second active sites, respectively), the energy difference between two carbonium ions, are highly correlated to the activity (logK). Also, we can see that $\Delta E_{1,s}$, $\Delta E_{2,f}$, and $\Delta E_{2,s}$ have a good correlation with the activity. In the meantime, we notice that logP(o/w) has a very low correlation with the activity.

We used these descriptors to perform multiple regression analysis and construct QSAR models to explore the relation-

Table 1. Calculated Energies of the First and Second Active Sites of a Set of 48 PAHs ($eV \cdot mol^{-1}$)[a]

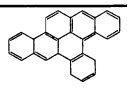
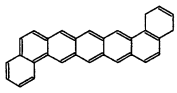
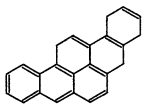
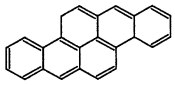
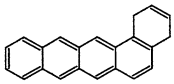
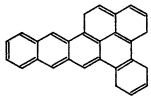
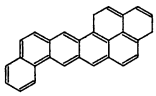
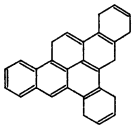
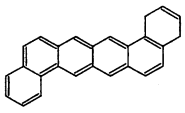
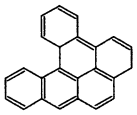
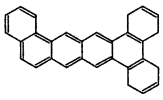
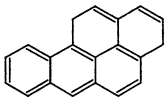
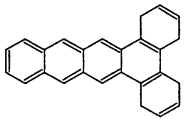
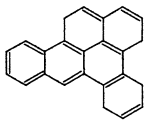
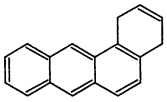
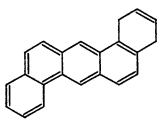
Compound	Structure	$\Delta E_{2,f}$	$\Delta E_{2,s}$	$\Delta E_{1,s}$	$\Delta E_{0,f}$	$\Delta E_{0,s}$
1		2.94	2.89	-1.03	0.44	0.45
2		2.73	1.98	-1.29	0.17	0.050
3		2.80	2.80	-0.875	0.48	0.48
4		2.76	2.71	-0.646	0.36	0.50
5		2.66	1.98	-0.830	0.22	0.050
6		2.80	2.65	-0.883	0.41	0.15
7		2.81	2.64	-0.745	0.65	0.26
8		2.93	2.93	-1.08	0.53	0.53
9		2.70	1.98	-1.29	0.23	0.050
10		2.98	2.78	-0.982	0.22	0.62
11		2.68	2.64	-1.088	0.14	0.13
12		2.65	2.56	-0.695	0.48	0.43
13		2.68	2.68	-1.10	0.11	0.11
14		2.66	2.60	-0.783	0.25	0.45
15		2.53	2.36	-0.897	0.19	0.10
16		2.51	2.33	-0.656	0.12	0.11

Table 1. (Continued)

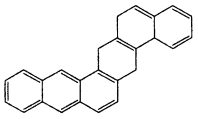
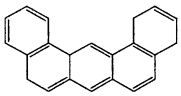
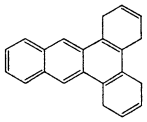
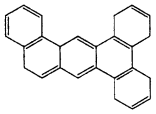
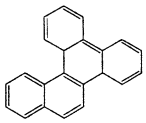
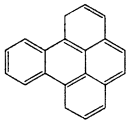
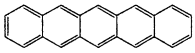
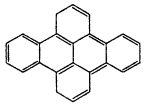
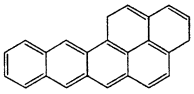
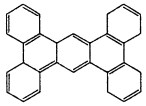
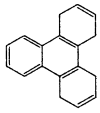
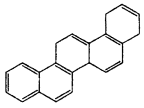
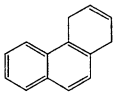
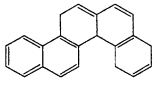
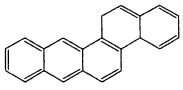
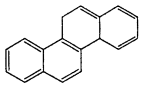
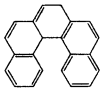
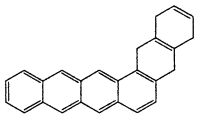
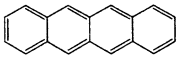
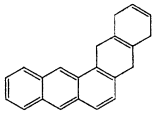
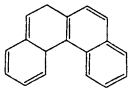
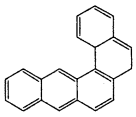
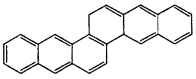
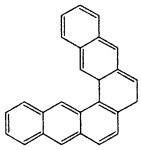
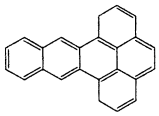
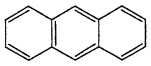
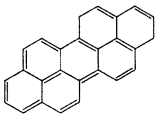
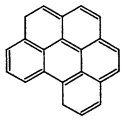
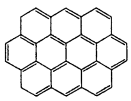
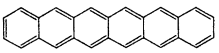
Compound	Structure	$\Delta E_{2,f}$	$\Delta E_{2,s}$	$\Delta E_{1,s}$	$\Delta E_{0,f}$	$\Delta E_{0,s}$
17		2.57	1.98	-1.29	0.12	0.050
18		2.50	2.50	-0.965	0.14	0.14
19		2.58	2.58	-1.08	0.12	0.12
20		2.66	2.56	-1.03	0.17	0.20
21		2.74	2.59	-1.02	0.42	0.15
22		2.52	1.98	-1.29	0.10	0.050
23		2.60	1.98	-1.29	0.16	0.05
24		2.54	2.54	-1.05	0.10	0.10
25		2.77	2.64	-0.704	0.63	0.34
26		2.59	2.59	-1.06	0.10	0.10
27		2.47	2.47	-1.04	0.10	0.10
28		2.41	2.45	-0.734	0.070	0.31
29		2.34	2.34	-0.953	0.11	0.11
30		2.59	2.48	-0.423	0.20	0.43
31		2.42	2.50	-0.673	0.030	0.37
32		2.44	2.43	-0.780	0.33	0.33
33		2.64	2.54	-0.764	0.28	0.26

Table 1. (Continued)

Compound	Structure	$\Delta E_{2,f}$	$\Delta E_{2,s}$	$\Delta E_{1,s}$	$\Delta E_{0,f}$	$\Delta E_{0,s}$
34		2.66	1.98	-1.29	0.040	0.050
35		2.49	1.98	-1.29	0.18	0.050
36		2.55	1.98	-1.29	0.12	0.050
37		2.32	2.32	-0.776	0.15	0.15
38		2.54	1.98	-1.29	0.11	0.050
39		2.50	1.98	-1.29	0.16	0.050
40		2.50	2.50	-0.723	0.11	0.11
41		2.47	1.98	-1.29	0.12	0.05
42		2.34	2.34	-0.697	0.20	0.20
43		2.15	2.15	-0.832	0.18	0.18
44		2.82	2.82	-0.653	0.62	0.62
45		2.54	2.54	-0.752	0.32	0.32
46		2.72	1.98	-1.29	0.050	0.050
47		2.67	1.98	-1.29	0.11	0.050
48		2.76	2.76	-0.903	0.10	0.10

[a] $\Delta E_{1,s}$ − f denotes energy change on the first active site, s denotes the energy changes on the second active site.

ship between the energy terms and the activities of the PAHs. The results show that there is no observable difference between the models with and without logP because of its low correlation to activity. LogP is normally used to indicate the proportion of an agent that reaches the biologic target in vivo. All of these PAHs are very structurally similar and consist of just two types of atoms, hydrogen and aromatic carbon. Most of them are or are nearly planar. The similar logPs do not account for the distinct difference in carcinogenicity of these PAHs. Therefore this term will not be used in further analyses. The best regression model is shown below. The regression coefficient (R) of the model is 0.77. In the regression model, two outliers (no. 12 and 44) were recognized. If the two outliers are excluded from the model,

Table 2. Correlation Matrix of Variables from Factor and Principal Analysis

	LogK	$\Delta E_{1,s}$[a]	$\Delta E_{2,f}$	$\Delta E_{2,s}$	$\Delta E_{0,f}$	$\Delta E_{0,s}$	LogP(o/w)[b]
logK	1						
$\Delta E_{1,s}$	0.44	1					
$\Delta E_{2,f}$	0.47	−0.07	1				
$\Delta E_{2,s}$	0.61	0.59	0.46	1			
$\Delta E_{0,f}$	0.52	0.40	0.55	0.54	1		
$\Delta E_{0,s}$	0.74	0.62	0.44	0.72	0.64	1	
LogP(o/w)	0.11	−0.31	0.63	0.05	0.17	0.04	1

[a] $\Delta E_{1,s}$ − f denotes energy change on the first active site, s denotes the energy changes on the second active site. [b] Calculated by MOE.

the new regression model produces better results with a regression coefficient of 0.81.

$$\text{activity} = -4.06 + 1.32\Delta E_{1,s} + 0.348\Delta E_{2,f} + 0.429\Delta E_{2,s} + 0.341\Delta E_{0,f} + 3.74\Delta E_{0,s} \ldots \quad (3)$$

Furthermore, cross-validations (leave-one-out) were performed on both sets of data. The cross-validation coefficients (q) are 0.70 (whole set of data) and 0.75 (excluding two outliers). The activity of the PAHs predicted by cross-validation is listed in Table 3.

To compare to observed activity, the calculated activity was normalized to the five-level index. The result shows that of 48 studied PAHs, 36 have the same level of predicted activities compared to observed activities, 10 have one level of difference, and 2 outliers have two levels of difference. With a tolerance of 0, the accuracy of the model prediction is 75%, while with a tolerance of 1, the accuracy of the model prediction is 96%. The results demonstrate that the model can predict the activity of PAHs well. As stated above, we cannot exactly quantify the carcinogenic activity of PAHs and use a discrete activity at equal interval in our model. As expected, we did not get a highly quantitative model with a high coefficient. Therefore the model should be regarded as semiquantitative only. The predictive ability of the model were further analyzed using binary QSAR model in MOE. The total accuracy, accuracy on active, and accuracy on inactive predicted by cross-validation (leave-one-out) of the binary model with all compounds are 88%, 83%, and 92%, respectively. The accuracies of the model without outliers are 92%, 86%, and 96%, respectively. The model demonstrates a good ability to distinguish noncarcinogenic PAHs from carcinogenic PAHs.

The difference between E_2 and E_1 can be used to indicate the relative stability of the epoxide, and the difference between E_3 and E_2 can be used to indicate the relative stability of the carbonium ion. The epoxyl-energies of two active sites, $\Delta E_{1,f}$ and $\Delta E_{1,s}$, are similar to the localization energy. The lower the energy, the more stable the epoxide. The cationized-energies of two active sites, $\Delta E_{2,f}$ and $\Delta E_{2,s}$, are similar to the delocalization energy. The lower the energy, the greater probably a carbonium ion forms and then reacts with a nucleophilic agent (S_N1). Accordingly, the energies can be treated as a measurement for reactivity of an epoxide with a nucleophilic agent through an S_N1 mechanism. The $\Delta E_{0,f}$ and $\Delta E_{0,s}$ energies are the energy differences between two possible carbonium ions (Figure 1 (1) and (2)) of two active sites. The higher the energy, the more probable a partial-charge will develop on a carbon and then react with a nucleophilic agent (S_N2). Accordingly, the energies quantify the relative reactivity of an epoxide with a nucleophilic agent through an S_N2 mechanism. Actually, most SN reactions are a combination of the two mechanisms. Therefore, our model based on these energies can be treated as a description of the relative reactivity of an epoxide of PAH with a nucleophilic agent. In other words, only the relative thermodynamic stabilities of these metabolized intermediates are related to the carcinogenicity of PAHs in the model.

In the model, not only does the first active site of the PAHs contribute to their activities but also the second active site. This is consistent with the fact that more and more adducts on other positions, in addition to the most probable Bay-region, have been found in experiments. All the active sites are important to PAH carcinogenesis. Because active intermediates are initially activated by enzymes, the activated

Table 3. Predicted Activity of 48 PAHs by the Model Compared with Observed Activity

compd	obsd activity index	pred activity index[a]	pred activity
1	++	++	2.37
2	-	-	0.17
3	++++/+++	++	2.36
4	++++/+++	++	2.42
5	-	-	0.36
6	+	+	1.13
7	+	+	1.63
8	++	++	2.64
9	-	-	0.16
10	+++	+++	2.97
11	+	+	0.73
12	++++	++	2.00
13	++	+	0.67
14	+++	++	1.98
15	-/+	-	0.47
16	++	+	0.56
17	-	-	−0.04
18	++	+	0.56
19	-/+	+	0.58
20	-	+	0.95
21	+	+	1.00
22	-	-	−0.08
23	-	-	0.03
24	±	-	0.42
25	++	++	1.90
26	-	-	0.50
27	-	-	0.34
28	-	+	1.08
29	-	-	0.21
30	++	++	1.94
31	-	+	1.33
32	+	+	1.25
33	-	+	1.31
34	-	-	0.06
35	-	-	−0.09
36	-	-	−0.04
37	±	-	0.385
38	-	-	−0.06
39	-	-	−0.13
40	-	-/+	0.54
41	-	-	−0.17
42	-	-	0.47
43	-	-	0.21
44	+	+++	2.99
45	++	++	1.68
46	-	-	0.12
47	-	-	0.10
48	-/+	+	0.97

[a] The predicted activity index is based on predicted activity values: ++++ for $K > 3.0$, +++ for $2.7 < K < 3.0$, ++ for $1.66 < K < 2.7$, + for $0.56 < K < 1.65$, and − for $K < 0.55$.

positions are normally decided by these enzymes. At the same time, we find that there is a favorable distance between the two active sites. The characteristics of bielectrophilic active sites together with the specific structural character may be important to explore and understand the interaction of PAH with DNA.

CONCLUSION

Based upon proposed metabolic reaction processes, the energy changes related to π orbital delocalization and the energy difference between two carbonium ions have been calculated by a semiempirical quantum method (AM1). A QSAR model of carcinogenesis of PAHs is developed, which reasonably describes the carcinogenic activity of the studied PAHs and can distinguish between carcinogenic PAHs and noncarcinogenic PAHs. The study demonstrates that the relative thermodynamic stabilities of epoxide and carbonium intermediates of PAHs can be used to describe the carcinogenicity of PAHs. The energy terms used in the model can be related to two nucleophilic reactions (S_N1 and S_N2).

The concept of using double active sites in the model is consistent with the fact that DNA adducts can be formed at different positions of a carcinogenic PAH. The work shows that both sites are important to the carcinogenicity of PAHs. Also it indicates that the distance between the two active sites can be used as a factor to determine chemical carcinogenicity of PAHs. This helps to understand the interactions of the ultimate metabolites of PAHs with enzymes and DNA. These results, together with experimental findings, suggest that not only the active site on the Bay-region but also active sites on other regions are important for us to understand the mechanism of chemical carcinogenesis of PAHs.

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