Theoretical studies on the carcinogenic activity of diol epoxide derivatives of PAH: proton affinity and aromaticity as decisive descriptors†

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A comparative study between bay-region and nonbay-region diol epoxide (DE) derivatives of seventeen carcinogenic polycyclic aromatic hydrocarbons (PAHs) was carried out using the B3LYP/6–31G(d,p) level of density functional theory to understand the factors responsible for the increased carcinogenic activity of bay-region derivatives. Molecular electrostatic potential analysis as well as proton affinity calculations showed that the epoxide sites of bay-region derivatives are much more reactive than the corresponding nonbay-region analogs. The charge delocalization mode in the carbocation intermediates resulting from the protonation reactions was followed through LUMO analysis. The relative aromaticity in the different rings in the arenium ions was gauged by NICS(1)$_{zz}$ computations. Both these calculations revealed that the protonated DEs (DEH^+) are stabilized by higher aromaticity in the bay-region derivatives than the nonbay-region derivatives. Hence, a bay-region DEH^+ can be retained in the reacting medium for a longer time than compared with the DEH^+ formed from a nonbay-region DEs. Thus the high carcinogenic activity of bay-region DEs is attributed to the high reactivity of the epoxide system for protonation and the high thermodynamic stability of the resulting cation. Multiple regression analysis also confirms the above results wherein proton affinity and aromaticity significantly explain the variations in the carcinogenic activity of the molecules under study.

Introduction

Polycyclic aromatic hydrocarbons (PAHs) belong to a class of environmental pollutants having different biological effects.[1] Some of the members are found to be potent animal carcinogens while others are found to be inactive upon testing. The carcinogenic PAHs owe most of their biological activity to their ability to be metabolized to highly reactive benzo-ring diol-epoxides where the oxirane ring is part of the bay-region of the hydrocarbon.[2] A bay-region occurs in a PAH when an angularly fused benzo-ring is present as in phenanthrene. Typical examples of two different bay-region diol epoxides (bDEs) are given along with nonbay-region diol epoxides (nbDEs) in Fig. 1. The bDE notation suggests that one of the bay region carbon atoms is part of the epoxide ring and in the case of nbDEs, the 'nb' only indicates that the epoxide ring is not part of the bay region.

The bay-region DE of benzo[*a*]pyrene (BaP), which is an extensively studied PAH, has two diastereomeric forms. One has the distal hydroxyl group and the epoxide oxygen in the anti position and the other has them in syn positions. Depending on the orientation of the hydroxyl groups relative to one another, each diastereomeric bDE can be resolved into two pairs of optical enantiomers. These four structures are given in Fig. 2. Among these structures,

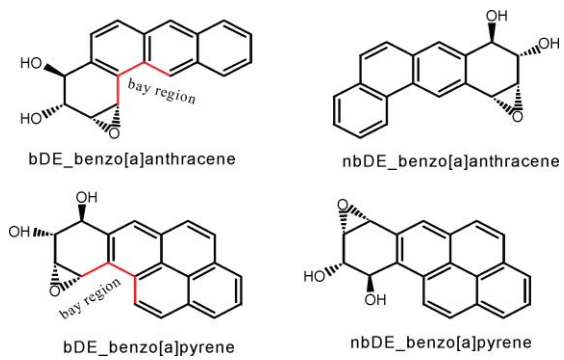

Fig. 1 Bay- and nonbay-region dihydrodiol epoxide derivatives of PAHs.

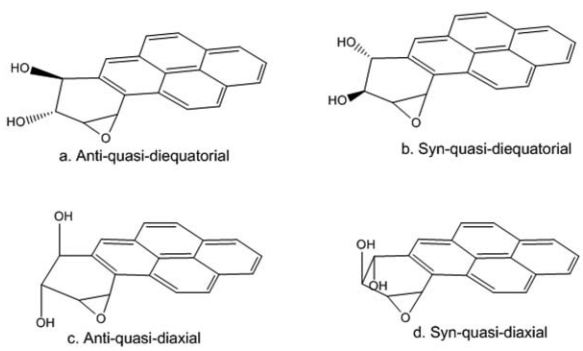

Fig. 2 Four diastereomers of the diol epoxide derivative of benzo[*a*]-pyrene.

experimental evidence[3,4] as well as theoretical calculations[5] show that the syn conformation with two hydroxyl groups lying nearly

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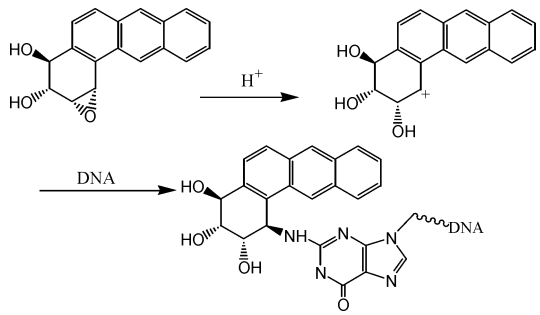
† Electronic supplementary information (ESI) available: SCF energies, zero point energies, and enthalpy values. NICS(1) and NICS(1)$_{zz}$ values of all the aromatic rings in bay- and nonbay-region DEH^+ systems. See DOI: 10.1039/b813008f



Scheme 1 Formation of electrophilic species in the metabolic activation of benzo[*a*]anthracene.

perpendicular to the plane (syn-quasi-diaxial) and the anti conformation with two hydroxyl groups lying nearly in the plane of the remainder of the molecule (anti-quasi-diequatorial) have lower energy (Fig. 2a and b). Studies have shown that the most mutagenic and carcinogenic of these is (7*R*,8*S*)-dihydroxy-(9*S*,10*R*)-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (Fig. 2b) and this isomer is also the one formed in highest amounts *in vivo*.[6,7]

Once the PAH DE is formed by metabolic processes, hydrolysis of the epoxide ring can occur through attack of a water molecule on the epoxide ring or through a DNA-mediated, acid catalyzed reaction in which initial attack by a proton on the epoxide oxygen opens the epoxide ring, forming a carbocation (*cf.* Scheme 1).[8,9] The electron deficient species thus formed would react with the nucleophilic sites in DNA (mostly the exocyclic amine groups of adenine and guanine) resulting in the formation of stable DNA adducts often leading to mutation and cancer.[10,11]

Many theoretical studies related to the electronic, structural and mechanistic features associated with the carcinogenic activity of PAH dihydrodiol epoxides have been carried out by several researchers.[12–21] Most of the earlier works gave support to the experimental observations of bay-region theory, considering individual PAHs mainly using semi empirical or *ab initio* methods with small basis sets while the later works stresses the substitution effects. Our recent work on the carcinogenicity of PAHs supported the bay-region reactivity by identifying the bay-region as the most electron dense centre in the molecule.[22] In the present study, we will mainly focus on the molecular electrostatic potential (MESP) and aromaticity features of the bDEs, nbDEs, and their corresponding protonated forms in the selected carcinogenic PAH molecules. Further, the proton affinities of the set of 17 carcinogenic molecules (*cf.* Fig. 3) having bay-regions are compared with their nonbay analogues employing DFT methods. Interrelationship was sought between the experimental carcinogenic potency reported in the literature and the calculated proton affinity and electronic properties.

Computational methods

The geometries of all the structures were fully optimized with the Gaussian-03[23] suite of programs using the hybrid B3LYP[24–26] method with a 6–31G(d,p) basis set and all the structures were confirmed as minima by vibrational frequency calculations. The theoretical predictions for proton affinities were performed at the same level of theory. Since proton affinity is defined as the standard enthalpy per mole of the protonation reaction at 298 K, it is

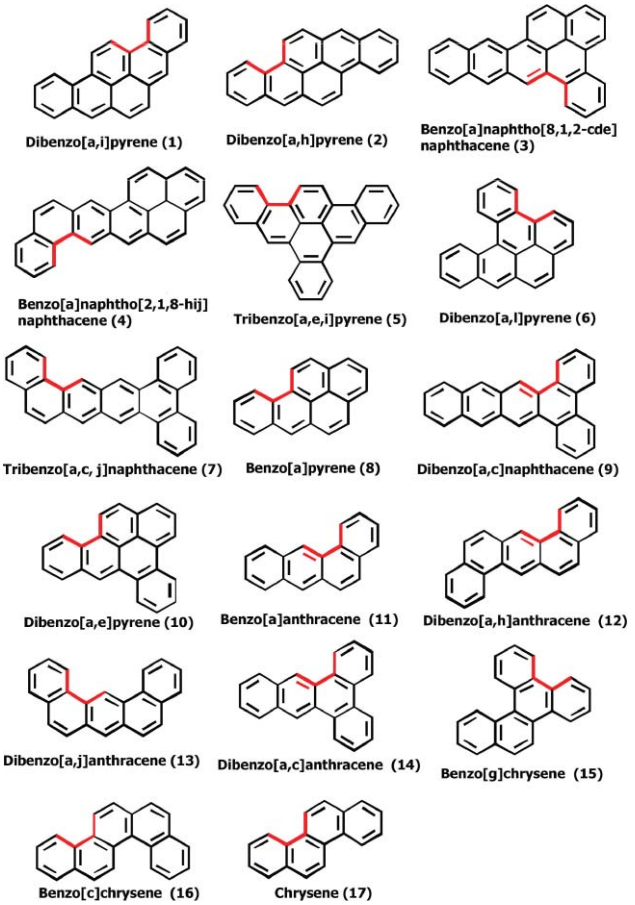


Fig. 3 Parent PAH molecules possessing bay-regions (in red color) selected for this study. The numbers in the round brackets are the serial numbers used in all the tables to represent the molecules.

calculated here as the negative value of change in the enthalpy of protonation of PAH DEs. The set of molecules given in Fig. 3 was selected based on the availability of carcinogenic indices. The nucleus independent chemical shift (NICS) values, which were proposed as a reliable criterion of aromaticity,[27,28] were also calculated using the gauge-independent atomic orbital (GIAO)[29] method at the B3LYP/6–31G(d,p) level of theory. The NICS values were calculated at 1Å above the centre of the six membered rings and the notation NICS(1)[28] is used to designate them. Recent research in NICS based criteria of aromaticity suggest that the magnitude of the tensor of the NICS(1) perpendicular to the plane of the ring system (designated as $NICS(1)_{zz}$)[30,31] is a better measure of the aromaticity of polycyclic species than NICS(1). Therefore, we used $NICS(1)_{zz}$ values in the present work to quantify the aromaticity of six membered rings.

For all the molecules, the DFT level wave function is used to calculate the scalar field of molecular electrostatic potential (MESP).[32–36] The MESP, $V(\mathbf{r})$, at a point $\mathbf{r}$ due to a molecular system with nuclear charges Z_A located at $\mathbf{R}_A$ and the electron density $\rho(\mathbf{r})$ is defined as

$$V(\mathbf{r}) = \sum_{A}^{N} \frac{Z_A}{|\mathbf{r} - \mathbf{R}_A|} - \int \frac{\rho(\mathbf{r}')\mathrm{d}^3\mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|} \quad (1)$$

where N is the total number of nuclei in the molecule. This quantity is defined as the energy required for bringing a test positive charge from infinity to a point **r** at the unperturbed ground state of the molecule and the topological features of MESP are widely used as descriptors of molecular reactivity.[37–41]

Results and discussions

To understand the relative stability of the four different configurations of diol epoxide derivatives (*cf.* Fig. 2) in terms of their total energy, we have modeled the bay-region diol epoxide system of phenanthrene, the simplest PAH system having a bay-region. The optimized structures are depicted in Fig. 4 along with their relative energy values. The stability of the different diastereomers is found to be decreasing in the order syn-quasi-diaxial > anti-quasi-diequatorial > anti-quasi-diaxial > syn-quasi-diequatorial. The difference in energy between the lowest energy syn-quasi-diaxial and anti-quasi-diequatorial forms is only 0.25 kcal/mol. The presence of an $OH\cdots O_{epoxy}$ hydrogen bond (*cf.* Fig. 4) provides anchimeric assistance to the syn-quasi diaxial isomer (structure a) to enable it to react with water and other nucleophiles more rapidly than the anti-isomers, thereby reducing the presence of ring opened cationic species which are essential for forming strong covalent bonds with the DNA bases.[42] Hence, the second stable structure with the anti-quasi-diequatorial conformation with (*R*,*S*)-diol (*S*,*R*)-epoxide absolute configuration (structure b) is used to construct the diol epoxide derivatives of all the PAHs used in the study and is also reported to be the most mutagenic isomer.[6,7]

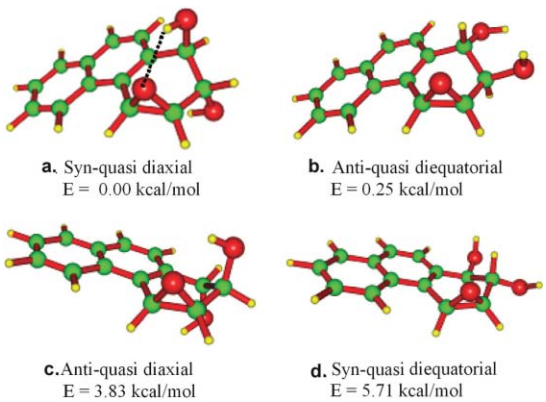


Fig. 4 Stereo isomers of bay-region diol epoxide derivatives of phenanthrene. The relative energy (E) of each conformer with respect to conformer (a) is shown.

Molecular electrostatic potential analysis

It may be noted that the lone pair and π bond region in a molecule is characterized by negative valued MESP while the region closer to the nuclei is characterized by positive valued MESP.[36] Therefore, the spatial distribution and the electrostatic potential values can be used to determine the probable site of attack of an electrophile or nucleophile as the primary chemical reaction event.[39] In the case of DE systems, the reactivity of bay-region DEs over nonbay DEs is conveniently assessed by the calculation of the most negative-valued MESP (designated as V_{min}) in the epoxide lone pair region. This approach is justifiable because the epoxide oxygen is vulnerable to attack by protons and the V_{min} measures the potential energy of a test positive charge at the lone pair site.

Table 1 V_{min} values of bay- and nonbay-region epoxy oxygens for selected PAHs

PAH-DE Systems of	V_{min} values (kcal/mol)	
	Bay	Nonbay
Dibenzo[a,i]pyrene (**1**)	–37.46	–37.21
Dibenzo[a,h]pyrene (**2**)	–37.53	–36.90
Benzo[a]naphtho[8,1,2-cde]naphthacene (**3**)	–37.15	–37.15
Benzo[a]naphtho[2,1,8-hij]naphthacene (**4**)	–37.34	–37.34
Tribenzo[a,e,i]pyrene (**5**)	–37.65	–36.90
Dibenzo[a,l]pyrene (**6**)	–36.27	–35.77
Tribenzo[a,c,j]naphthacene (**7**)	–37.59	–37.46
Benzo[a]pyrene (**8**)	–37.84	–37.27
Dibenzo[a,c]naphthacene (**9**)	–37.59	–37.21
Dibenzo[a,e]pyrene (**10**)	–37.78	–37.09
Benzo[a]anthracene (**11**)	–37.96	–37.40
Dibenzo[a,h]anthracene (**12**)	–37.71	–37.21
Dibenzo[a,j]anthracene (**13**)	–37.27	–37.53
Dibenzo[a,c]anthracene (**14**)	–37.59	–36.90
Benzo[g]chrysene (**15**)	–37.59	–36.14
Benzo[c]chrysene (**16**)	–37.90	–37.59
Chrysene (**17**)	–37.46	–37.46

The V_{min} value at the epoxy oxygen is given in Table 1 for both bay- and nonbay-region DEs. A comparison of the V_{min} values clearly suggests that the V_{min} is larger in magnitude for all the bay-region epoxy oxygens except for the diol epoxide of dibenzo[a,j]anthracene. Interestingly, the difference in V_{min} values between bay- and nonbay-region epoxy oxygens (ΔV_{min}) is more pronounced in the highly potent carcinogens (*cf.* Table 2). At the same time, weak carcinogens like chrysene, benzo-[a]naphtho[8,1,2-cde]naphthacene, and benzo[a]naphtho-[2,1,8-hij]naphthacene showed the same value of V_{min} for both bay- and nonbay-derivatives. A comparison of the MESP features of the bay and nonbay system of benzo[a]pyrene is illustrated in Fig. 5. Thus the V_{min} analysis suggests that bay-region epoxy oxygens are more reactive than their nonbay analogues towards electrophiles. The increased reactivity of the bay- region diol epoxides had also

Table 2 The proton affinity (PA) of bay- and nonbay-region diol epoxide derivatives of PAH. See Table 1 for names of the compounds and Fig. 3 for the parent PAH systems

DE systems of	PA of bay DE	PA of nonbay DE	ΔPA	CA
1	241.7	227.8	13.9	++++
2	240.1	227.1	13.0	++++
3	238.0	235.7	2.3	+
4	241.1	236.2	4.9	+
5	241.5	229.1	12.4	++
6	241.1	229.0	12.1	+++
7	238.9	238.7	0.2	+
8	238.7	224.4	12.3	++++
9	236.9	230.3	6.6	++
10	237.6	226.7	10.9	+++
11	232.6	225.9	6.7	+
12	233.9	232.3	1.6	++
13	232.9	233.7	–0.8	++
14	233.2	227.2	6.0	+
15	234.4	231.6	2.8	+
16	230.5	230.6	–0.1	+
17	227.3	225.9	1.4	+

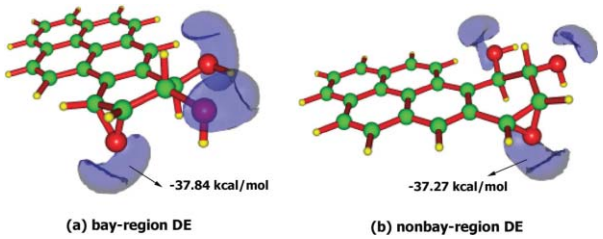


Fig. 5 V_{min} values of the epoxy oxygens in benzo[a]pyrene DEs at an isosurface value of –25.1 kcal/mol. The depicted values are for the V_{min} points.

been attributed as the basis for the increased mutagenicity of PAHs in the earlier studies.[16,19,21]

Proton affinity calculations

The proton affinity (PA) of a diol epoxide is defined as the negative of the change in enthalpy (ΔH) at 298K in the gas phase reaction between a proton and the diol epoxide concerned, to give the conjugate acid tetrahydrotriol carbocation (*cf.* Scheme 1). It was found that the ΔH values become increasingly exothermic as the number of rings increases (see the ESI† for details). In order to calculate the PA, the enthalpy values of both bay and nonbay diol epoxide derivatives as well as their protonated forms at the O_{epoxy} site were determined at the B3LYP/6–31G(d, p) level for all the selected carcinogenic PAHs. The PA values are presented in Table 2. As we can see, in general all the bDE systems showed significantly higher PA values than their nbDE systems, especially for highly carcinogenic molecules. For instance, the PA of bDE of benzo[a]pyrene is 238.7 kcal/mol while it is 224.4 kcal/mol for nbDE. On the other hand, for the weakly carcinogenic molecules like chrysene, the PA values are 227.3 kcal/mol and 225.9 kcal/mol, for bDE and nbDE respectively. However, systems **13** and **16** are exceptions as their PA values are slightly higher for the nbDE.

In Table 2, the difference between the proton affinity (ΔPA) of the bDE and corresponding nbDE of various PAHs is correlated with their reported carcinogenic activity (CA) index. Since the CA of PAHs varies with animal as well as the route of exposure, Badger's + index system (++++, +++, ++, +) which specifies the range of CA as very high, high, moderate and weak respectively,[43,44] was used to denote the activity of the PAHs rather than numerical Iball indices.[45] From Table 2, it is very clear that all the molecules that are classified as highly carcinogenic molecules, with a carcinogenic index denoted by ++++/+++, have a remarkable difference in proton affinity (ΔPA) between bay and nonbay DE derivatives (more than 10 kcal/mol). The exceptional behavior of dibenzo[a,j]anthracene (**13**) is attributed to the reduced bay-region carbocation delocalization energy due to the adjacent kinks present in the molecule as pointed out by Lowe and Silverman.[46] In the case of benzo[c]chrysene (**16**), a molecule possessing both bay and fjord regions, diol epoxides at both the regions are reported to be formed as intermediates in metabolism.[47] However the bay-region diol epoxides are found to be inactive upon testing, which is in agreement with the calculated negative value of ΔPA in the present study.[48] From earlier studies, Jerina and Lehr showed that a simple MO index derived from the delocalization energy change for the transformation of DEs to a bay-region carbonium ion, was useful in evaluating the relative ease of formation of a carbocation and hence the carcinogenic activation.[49] Here we have demonstrated that the ΔPA of DEs of bay and nonbay derivatives calculated at a higher level of theory is a better measure of carcinogenicity.

Molecular orbital analysis

The bay-region systems showed more delocalized HOMO and LUMO orbitals than their nonbay-region counterparts and therefore the formation of the open carbocation was more favored in bDEs as the positive charge at the benzylic carbocation is diminished by delocalization into the π system. This observation also supported the greater ease of carbonium ion formation in the bDEs than the nbDEs. In Fig. 6, the LUMO pictures of the cations in the diol epoxide series are depicted and clearly suggest that the more localized LUMO in the nbDE is more highly reactive towards nucleophiles than the corresponding bDE. It means that the bay-region derivatives must be available in the cell media for a longer time for nucleophilic attack by the nucleic acid bases while the highly reactive nonbay-region derived carbocations might be undergoing hydrolysis to tetrols. The importance of the electronic stabilization of benzylic carbocations derived from bay-region DEs in contributing to their carcinogenic potency as well as chemical reactivity has been pointed out in earlier studies by Jerina and coworkers.[49] However, their computed delocalization energies derived from the Huckel MO method could not correlate the reported tumorigenic potency.[50]

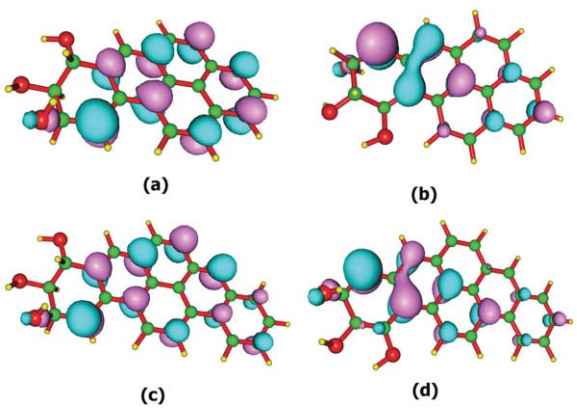


Fig. 6 LUMO plots of (a) bay- and (b) nonbay-region protonated DEs of benzo[a]pyrene and (c) bay- and (d) nonbay-region protonated DEs of dibenzo[a,i]pyrene.

NICS based analysis of aromaticity

It is expected that the marked differences in the delocalization of the positive charge in bay- and nonbay-region DEH^+ systems as seen from their LUMO plots may also be reflected in the closely related phenomenon of aromaticity. For measuring aromaticity, the Nucleus Independent Chemical Shift (NICS) has been widely used as a reliable measure.[51] Hence, NICS calculations are applied in this study to gain some insight into the relative aromaticity in various rings in the selected DEH^+ derivatives of PAHs. The NICS values are measured at 1Å away from the ring center (NICS(1)) to reduce the contribution of the magnetic tensor from

σ electrons. Further, the component of the tensor perpendicular to the plane of the ring, termed as NICS(1)$_{zz}$, is considered in the calculation which is closely related to the π system and hence widely accepted as a refined measure of NICS based aromaticity. Ringwise, NICS(1)$_{zz}$ values show that metabolically activated rings are antiaromatic with a positive value in all the DEH$^+$ derivatives. A comparative analysis of bay and nonbay DEH$^+$ systems shows that rings in bay-region derivatives are much more aromatic than those in their corresponding nonbay-region analogues. This feature is illustrated in Fig. 7 with the example of dibenzo[a,i]-pyrene (**1**). For making an easy and direct comparison of the NICS values, the sum of NICS(1)$_{zz}$ values ($\sum$NICS(1)$_{zz}$)were computed and they are depicted in Table 3 (see the ESI† for NICS(1)$_{zz}$ values obtained for each ring in all the systems). Very recently, Mills *et al.*[52] have demonstrated the use of the $\sum$NICS(1)$_{zz}$ as a measure of total aromaticity. They also suggest that for comparing the aromaticity values of compounds with different sizes, the $\sum$NICS(1)$_{zz}$ can be divided by the square of the total area of the rings. In the present work we also adopt this normalization procedure, and the computed $\sum$NICS(1)$_{zz}$/ring area² values are also presented in Table 3 for both bay- and nonbay-region DEH$^+$ systems.

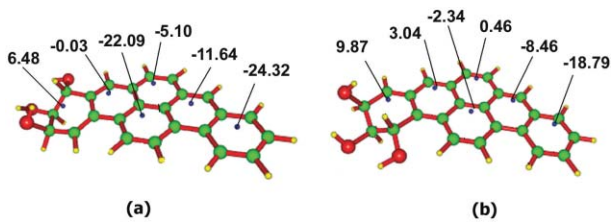


Fig. 7 NICS(1)$_{zz}$ values of a (a) bay- and (b) nonbay-region DEH$^+$ system.

The values of both $\sum$NICS(1)$_{zz}$ and NICS(1)$_{zz}$/ring area² clearly suggest that bay-region DEH$^+$ systems are significantly more aromatic than the corresponding nonbay-region DEH$^+$ systems. Importantly, the $\Delta\sum$NICS(1)$_{zz}$/ring area² values follow a nearly parallel trend to the observed carcinogenic activity of their parent PAHs which means that a DEH$^+$ system showing a high value of aromatic character is highly carcinogenic. For instance, for the highly carcinogenic systems **1**, **2**, **8**, **6**, and **10** given in Table 3, the calculated $\Delta(\sum$NICS(1)$_{zz})$/ring area² values are 0.040, 0.042, 0.042, 0.032, and 0.025, respectively and the corresponding Badger's '+' indices are '++++', '++++', '++++', '+++', and '+++'. On the other hand, most of the weakly carcinogenic system with a carcinogenic index of '+' showed $\Delta(\sum$NICS(1)$_{zz})$/ring area² values in the range of 0.008 to 0.019.

Table 3 NICS values of protonated dihydrodiol epoxide derivatives of 17 carcinogenic PAHs. See Table 1 for names of the compounds. See Fig. 3 for parent PAH systems

	Bay		Nonbay		
System	a1[a]	b1[a]	a2[a]	b2[a]	b2-b1
1	−56.71	−0.056	−16.24	−0.016	0.040
2	−61.46	−0.061	−19.15	−0.019	0.042
3	−79.08	−0.058	−64.25	−0.047	0.011
4	−81.84	−0.059	−40.25	−0.029	0.030
5	−74.54	−0.055	−33.85	−0.024	0.030
6	−51.64	−0.051	−20.14	−0.020	0.032
7	−75.15	−0.055	−58.03	−0.042	0.012
8	−40.94	−0.058	−11.70	−0.016	0.042
9	−66.77	−0.065	−43.92	−0.043	0.022
10	−55.20	−0.055	−30.30	−0.030	0.025
11	−36.36	−0.079	−27.92	−0.062	0.018
12	−51.69	−0.073	−32.52	−0.046	0.027
13	−49.95	−0.071	−36.39	−0.052	0.019
14	−47.04	−0.067	−33.57	−0.048	0.019
15	−39.49	−0.055	−33.69	−0.047	0.008
16	−56.83	−0.080	−37.25	−0.052	0.028
17	−37.10	−0.082	−21.75	−0.047	0.035

[a] a1 and a2 are the $\sum$NICS(1)$_{zz}$ values. b1 and b2 are the quantities corresponding to $\sum$NICS(1)$_{zz}$/ring area.[2]

Multiple linear regression analysis

The analysis presented so far clearly suggests that the carcinogenic activity of DE systems is directly related to the reactivity of the epoxide towards protonation as well as the aromatic stabilization of the resulting carbocation. Therefore, we considered these two key factors measured in terms of ΔPA (for proton affinity) and $\Delta(\sum$NICS(1)$_{zz})$/ring area² (for aromaticity) for a multiple linear regression (MLR) analysis to correlate with the expected '+' index values of carcinogenic activity. In order to do the MLR analysis, the '+' notations are converted to integer numbers so that each integer gives the number of '+' symbols in the Badger's index. The regression equation is found to be CA = 0.121261 (ΔPA) + 47.51856 ($\Delta(\sum$NICS(1)$_{zz})$/ring area²). The model gives a significant fit based on F value from ANOVA and the estimated regression coefficients are statistically significant at 5% level of significance. For this equation, the multiple correlation coefficient (R) has a value of 0.96. To examine the accuracy of the model in predicting out of sample observations, 'leave one out cross validation' was employed.[53] Here, the model is developed by leaving out one observation and then predicting the carcinogenicity of it. It is repeated for each observation and the accuracy is measured for all. Out of the sample predictions are accurate at 76.5%, implying that the changes in proton affinity (ΔPA) and aromaticity ($\Delta(\sum$NICS(1)$_{zz}$/ring area²) can be used as indicators for explaining the variations in carcinogenicity. The regression equation obtained for CA in this work clearly suggests that an increase in the ΔPA of DE as well as an increase in the $\Delta(\sum$NICS(1)$_{zz}$/ring area²) of DEH$^+$ causes an increase in the carcinogenic activity. In Fig. 8, the bar chart for the actual and predicted CA values is presented where the majority of them show a good agreement. However, notable differences can be seen in the

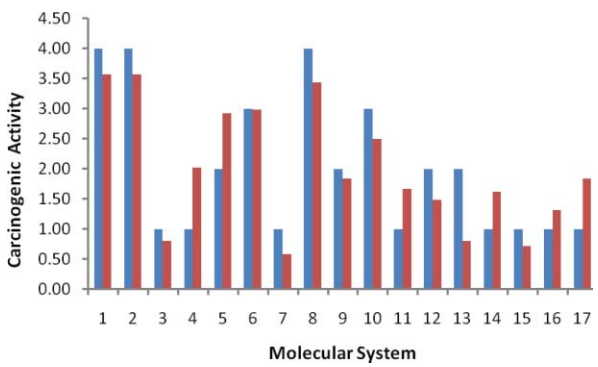


Fig. 8 Bar chart for carcinogenic activity (CA). Blue for actual and red for predicted values. See text for details.

CA values of systems **4**, **13**, and **17** where the predicted CA values of the first and last are higher while that of the second is lower than the expected CA values. It may be noted that the predicted values of CA are given with up to two decimal digits accuracy as this may further distinguish the finer variations in the carcinogenic activity of diol epoxides.

Conclusions

A multifaceted approach consisting of MESP analysis, proton affinity calculations, LUMO analysis, and NICS calculations has been utilized to explore the high carcinogenic activity of bay-region diol epoxide derivatives of PAHs. A comparative study between bay- and nonbay-region diol epoxides showed that the former compounds are more reactive towards protonation and their cationic intermediates are stabilized by higher aromaticity. The proton affinity values of DE systems and the NICS based aromaticity values of DEH^+ are correlated with the carcinogenic activity of diol epoxide derivatives of PAHs. The multiple linear regression equation obtained in this work strongly suggests that both proton affinity and aromaticity can be used as decisive descriptors for evaluating the carcinogenic activity of diol epoxide derivatives of PAH systems.

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