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Molecular Modelling Analyses of the Relative Stability of Alkenes, Arenes and Their Epoxides and Diols

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Polyaromatic hydrocarbons often acquire carcinogenicity as a result of their activation due to the formation of epoxides and diols. Epoxides are formed when an oxygen atom binds across a carbon-to-carbon double bond. In this study, molecular modelling analyses using molecular mechanics, semi-empirical calculations were carried out to investigate the relative stability of alkenes, arenes, their epoxides and diols. The results of calculation show that the formation of epoxides and diols are spontaneous with the Gibb's free energy changes (ΔG) being negative for both. The calculated results also show that the stability of the epoxide formed depends on the position of double bond at which oxygen binds, giving credence to the idea of site-specificity in metabolic activation.

Key Words: Epoxide, Diol, Molecular Modelling, PM3.

INTRODUCTION

Accumulated evidence indicates that covalent binding of reactive electrophilic carcinogens to DNA plays a significant role in chemical carcinogenesis[1] and that most chemical carcinogens require activation to electrophilic metabolites that can cause gene mutations. It is known that chemical mutagens and carcinogens can produce point mutations, frameshift mutations and chromosome aberrations in mammalian cells[2]. Polyaromatic hydrocarbons (PAHs) are among the many environmental toxins[3]. A large number of enzymes are involved in the metabolism of xenobiotics. PAHs are often oxidisized by cytochrome P450 oxidase to epoxides intermediates, which are converted with the aid of epoxide hydrolase to the ultimate carcinogens, diol-epoxides. It has been suggested that individual differences in the metabolic activation and detoxification of PAHs may influence cancer risk[4]. For example, benzo(a)pyrene is metabolized by cytochrome 450 oxidase to benzo(a)pyrene-7,8-epoxide which is hydrated, catalyzed by epoxide hydrolase, to form benzo(a)pyrene-7,8-diol[2]. Benzo(a)pyrene-7,8-diol is considered the proximate carcinogen as it must be further metabolized by cytochrome P450 to form the ultimate carcinogen, benzo(a)pyrene-7,8-diol-9,10-epoxide that binds to several bases in DNA. Benzo(a)pyrene-7,8-diol-9,10-epoxide is highly mutagenic in eukaryotic and prokaryotic cells and carcinogenic in rodents[2].

Although the degree of total covalent binding of genotoxic carcinogens to DNA is often found to correlate with tumorigenic activity, it is also found that for some carcinogens there is a strong correlation between formation of very specific DNA adducts and tumorigenicity[2].

It is believed that not only the chemical structure of the metabolites of PAHs but also their stereochemistry is an important determinant of their carcinogenicity. Many PAHs are metabolized to bay-region diol epoxides, an example of which is benzo(a)pyrene-7,8-diol-9,10-epoxide. In the light of differences in toxicity, carcinogenicity and mutagenicity of different epoxides and their metabolites, an important question to ask is: *"Are there any differences in the stability of different possible epoxides?"*

Some commonly used chemicals are also found to be toxic. For example, 1,3-butadiene (BD) which is a commonly used chemical in the manufacture of synthetic rubber and various plastics, has been shown to be a potent animal carcinogen and a probable human carcinogen[5]. It is believed that bioactivation of 1,3-butadiene also involves the formation of epoxide. The aim of the present study is to investigate the relative stability of the epoxides, diols and their parent hydrocarbons, in particular, to determine (1) whether epoxide formation is more favoured for some compounds than others and (2) whether there is any site-specificity in the formation of epoxides.

EXPERIMENTAL

This is an entirely modelling study in which the structures of aromatic hydrocarbons and alkenes including ethene, 1,3-butadiene, 1,3,5-hexatriene, benzene, toluene, styrene, naphthalene, anthracene, naphthacene, pentacene, hexacene, toluene, pyrene, benzo(a)pyrene (Fig. 1), their epoxides and diols were optimized based on molecular mechanics and PM3 semi-empirical calculations using the program HyperChem 7.0.[6] For the optimized structures, total energy and heat of formation were calculated based on PM3 single-point calculations. The RMS gradient was set as 0.01 as the termination condition. The number of occupied and unoccupied molecular orbitals was set as 1 and 0 in single-point calculations.

RESULTS AND DISCUSSION

Table-1 gives the energies as per MM^+ calculations, total energies and heats of formation obtained from single-point PM3 calculations, for the optimized structures of ethene, propene, 1,3-butadiene, 1,3,5-hexatriene, benzene, naphthalene, anthracene, naphthacene, pentacene, hexacene, toluene, pyrene, benzo(a)pyrene, phenanthrene, styrene, their various epoxides and corresponding diols, using the program HyperChem 7.0.[6] For ethene and propene the calculated values of heats of formation were 16.6 and 7.0 kcal mol^{-1}, respectively. The values for the corresponding epoxides and diols were: ethene-1,2-epoxide: –8.2 kcal mol^{-1}, ethane-1,2-diol: –98.7 kcal mol^{-1}, propene-1,2-epoxide: –16.7 kcal mol^{-1} and propane-1,2-diol: -105.9 kcal mol^{-1}. Thus, the enthalpy changes for the reaction:

$$\text{Ethene} + \tfrac{1}{2}O_2 \rightarrow \text{Ethene-epoxide}$$

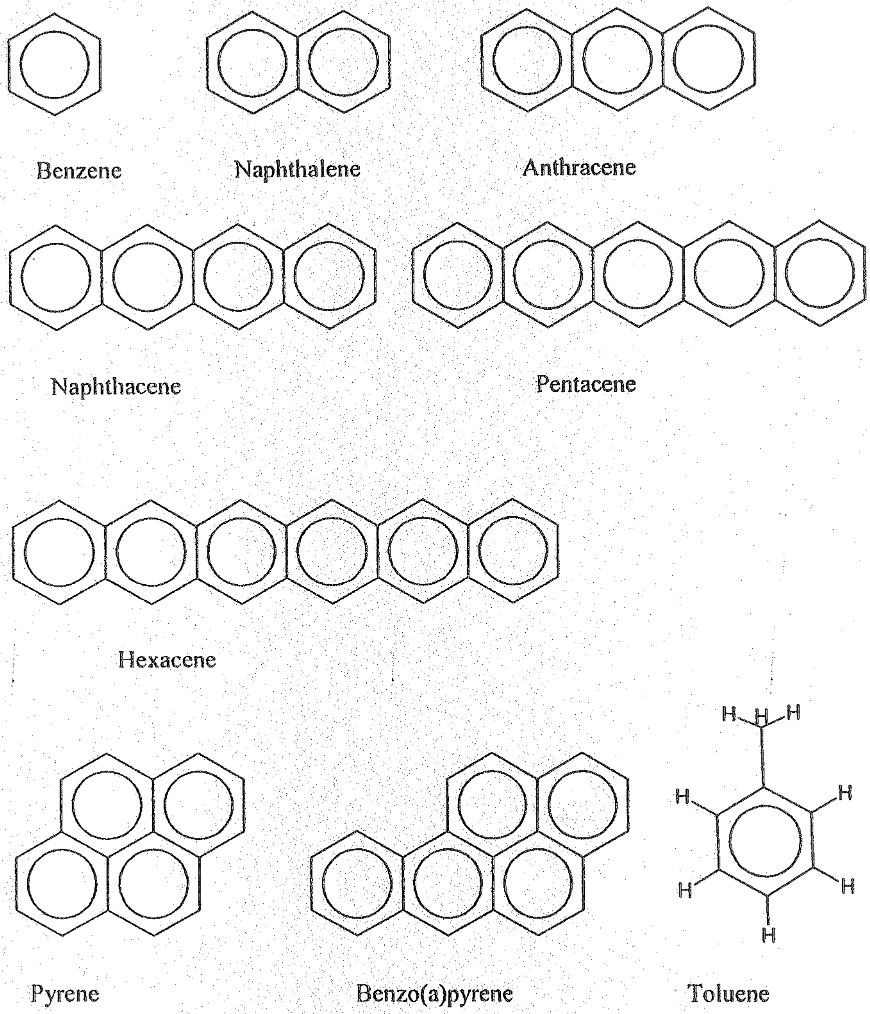

Fig. 1. Structures of various aromatic hydrocarbons

can be calculated as: $(-8+ 1/2 \times 0) - 16.6 = -24.2$ kcal mol^{-1}. Since entropy (which is a measure of randomness or chaotic condition in a system) is expected to decrease marginally in the formation of the epoxide, it may be seen that Gibb's free energy change ΔG (defined by the equation: $\Delta G = \Delta H - T\,\Delta S$, where ΔH is the change in enthalpy, ΔS is the change in entropy and T is the temperature in Kelvin) for the process would be negative. This means that formation of epoxide from ethene would be spontaneous (*i.e.*, the reaction would be possible from the thermodynamic viewpoint). Similarly, it is expected that Gibb's free energy changes for the formation of epoxide from propene and butadiene would also be negative since the enthalpy changes for the reactions are -23 and -21.9 kcal mol^{-1}, respectively. The reaction for the formation of ethane-1,2-diol from ethene-1,2-epoxide can be written as:

$$\text{Ethene-1,2-epoxide} + H_2O \rightarrow \text{Ethane-1,2-diol}$$

Taking the heat of formation of water as -68.3 kcal mol^{-1} ($= 285.8/4.186$), enthalpy change associated with the above reaction can be calculated as: $(-98.7) - (-8.2) + (-68.3) = -22.2$ kcal mol^{-1}. Assuming that when diol is formed epoxide, there would only be a small decrease in entropy, it can be seen that the Gibb's free energy change for the formation of ethane-1,2-diol from ethene-1,2-epoxide would be negative and hence the process would be spontaneous. It can be shown that the free energy for the formation of diol from epoxide is negative in all other cases, indicating that the diol formation reaction would be a spontaneous one. It should however be noted that in the absence of precise knowledge on entropy change, uncertainty remains in the conclusions reached applying to the spontaneity of epoxide and diol formation reactions. If the decrease in entropy is sufficiently large, it may very well be that neither the epoxide nor the diol formation reaction be spontaneous. What is more important is perhaps to note the difference in the ease of the two reactions and difference in the ease of epoxide formation for different compounds (*e.g.*, alkenes compared with aromatic hydrocarbons) and the existence of any site-specificity in the formation of epoxides. These are considered more fully in the following section.

The enthalpy change in the formation of epoxide from benzene is found to be much smaller than that in the formation of epoxide from ethene (+ 2.0 kcal mol^{-1} in the case of benzene as against –24.2 kcal mol^{-1} in the case of ethene). The small difference points to the extra stability of benzene as compared to alkenes such as ethene and propene, gained through delocalisation of π-electrons. This is generally found to be true for all other aromatic hydrocarbons considered in the present study. That is, the formation of epoxide from aromatic hydrocarbons is generally less favoured from the thermodynamic point of view than that from alkenes.

When the calculated values of heats of formation of anthracene (61.3 kcal mol^{-1}), anthracene-1,2-epoxide (52.9 kcal mol^{-1}), anthracene-2,3-epoxide (84.6 kcal mol^{-1}), anthracene-1,2-diol (–35.0 kcal mol^{-1}) and anthracene (8.2 kcal mol^{-1}) are considered, it is found that there is a site-specificity in the formation of epoxides and diols from anthracene-binding of oxygen at the 1,2-position is preferred over its binding at the 2,3-position. In the case of anthracene, naphthacene, pentacene and hexacene also, it is found that epoxides formed by binding of oxygen at different positions differ in heats of formation (Table-1), again indicating site specificity for binding oxygen across the double bond.

Similarly, it is found that there is a site-specificity in the formation of epoxides and diols from 1,3,5-hexatriene-binding to 1,2-position being preferred over binding to 3,4-position. Similar conclusions can be drawn in the case of benzo(a)pyrene (and toluene) as well. The heat of formation of benzo(a)pyrene-7,8-epoxide which is a known carcinogen is found to be significantly higher (by 14.5 kcal mol^{-1}) than that of benzo(a)pyrene-1,2-epoxide, indicating that benzo(a)pyrene-7,8-epoxide is an unstable high-energy molecule. A similar conclusion can be drawn for naphthacene-2,3-epoxide.

Charges on atoms

A question that may be asked is: "*Are there any differences in charges on atoms and if so do these reflect the greater stability of one epoxide over another?*".

Fig. 2 gives the charges on carbon atoms of anthracene along with 2D contour plots for the electrostatic potential.

TABLE-1
CALCULATED ENERGIES AND HEATS OF FORMATION OF COMPOUNDS

Parent mpound	MM⁺	PM3		Epoxide	MM⁺	PM3		Diol	MM⁺	PM3	
	Total energy (kcal mol^{-1})	Total energy (kcal mol^{-1})	ΔH$_f$ (kcal mol^{-1})		Total energy (kcal mol^{-1})	Total energy (kcal mol^{-1})	ΔH$_f$ (kcal mol^{-1})		Total energy (kcal mol^{-1})	Total energy (kcal mol^{-1})	ΔH$_f$ (kcal mol^{-1})
e	3.2	–6869.7	16.6	Ethene-1,2-epoxide	154.9	–13626.5	–8.2	Ethane-1,2-diol	0.4	–21156.2	–98.7
ne	2.3	–10322.4	7.0	Propene-1,2-epoxide	154.9	–17078.2	–16.7	Propane-1,2-diol	–3.5	–24606.6	–105.9
tadiene	–1.3	–13034.4	30.9	Butadiene-1,2-epoxide	157.7	–19788.4	9.0	3-butene-1,2-diol	7.6	–27314.4	–77.7
Hexatriene	1.2	–19197.7	46.7	Hexatriene-1,2-epoxide	153.1	–25952.1	24.4	3,5-hexadiene-1,2-diol	3.3	–33480.1	–64.4
				Hexatriene-3,4-epoxide	156.6	–25949.5	27.0	1,5-hexadiene-3,4-diol	6.6	–33470.9	–55.1
ne	–2.6	–18514.0	23.3	Benzene-1,2-epoxide	156.1	–25244.0	25.3	Benzene-1,2-diol	1.8	–32769.4	–60.8
halene	–6.4	–30147.5	40.8	Naphthalene-1,2-epoxide	155.1	–36864.7	55.7	Naphthalene-1,2-diol	1.7	–44387.5	–27.9
acene	–17.6	–41778.0	61.3	Anthracene-1,2-epoxide	225.4	–48518.5	52.9	Anthracene-1,2-diol	93.1	–56045.6	–35.0
				Anthracene-2,3-epoxide	227.4	–48486.8	84.6	Anthracene-2,3-diol	93.5	–56002.5	8.2
hacene	–24.2	–53406.4	83.9	Naphthacene-1,2-epoxide	139.6	–60146.9	75.5	Naphthacene-1 ,2-diol	–12.3	–67670.2	–8.6
				Naphthacene-2,3-epoxide	138.1	–60111.0	111.4	Naphthacene-2,3-diol	–17.4	–67633.1	28.5
cene	–32.4	–65028.4	112.9	Pentacene-1,2-epoxide	128.4	–71773.3	100.1	Pentacene-1,2-diol	–23.2	–79300.8	11.8

Parent ompound	MM⁺	PM3		Epoxide	MM⁺	PM3		Diol	MM⁺	PM3	
	Total energy (kcal mol^{-1})	Total energy (kcal mol^{-1})	ΔH_f (kcal mol^{-1})		Total energy (kcal mol^{-1})	Total energy (kcal mol^{-1})	ΔH_f (kcal mol^{-1})		Total energy (kcal mol^{-1})	Total energy (kcal mol^{-1})	ΔH_f (kcal mol^{-1})
				Pentacene-2,3-epoxide	133.5	–71735.9	137.5	Pentacene-2,3-diol	–26.0	–79258.0	54.6
cene	–41.9	–76654.0	138.3	Hexacene-1,2-epoxide	125.2	–83399.2	125.2	Hexacene-1,2-diol	14.1	–90923.3	40.4
				Hexacene-2,3-epoxide	123.3	–83361.1	163.3	Hexacene-2,3-diol	–34.5	–90881.2	82.5
ne	–2.8	–21966.5	13.9	Toluene-2,3-epoxide	236.8	–28697.2	15.3	Toluene-2,3-diol	–7.1	–36219.7	–68.0
				Toluene-3,4-epoxide	240.7	–28696.8	15.6	Toluene-3,4-diol	3.3	–32767.2	–58.6
le	–15.5	–47245.8	65.4	Pyrene-1,2-epoxide	144.8	–53274.9	68.4	Pyrene-1,2-diol	29.7	60710.3	65.0
o(a)pyrene	–19.3	–58878.3	83.9	Benzo(a)pyrene-1,2-epoxide	141.6	–65610.6	83.7	Benzo(a)pyrene-1,2-diol	76.9	–73132.1	1.5
				Benzo(a)pyrene-7,8-epoxide	220.3	–65596.2	98.2	Benzo(a)pyrene-7,8-diol	125.5	–73119.5	14.1
				Benzo(a)pyrene-7,8-epoxide-9,10-diol					323.2	–79890.1	–24.4
anthrene		–41784.1	55.2	Phenanthrene-1,2-epoxide	151.9	–48526.8	44.5	Phenanthrene-1,2-diol	–9.0	–56053.3	–42.7
ne	–1.6	–24677.3	39.0	1-phenylethane-1,2-epoxide	152.5	–31430.9	17.6	1-phenylethane-1,2-diol	–1.0	38955.8	–68.2

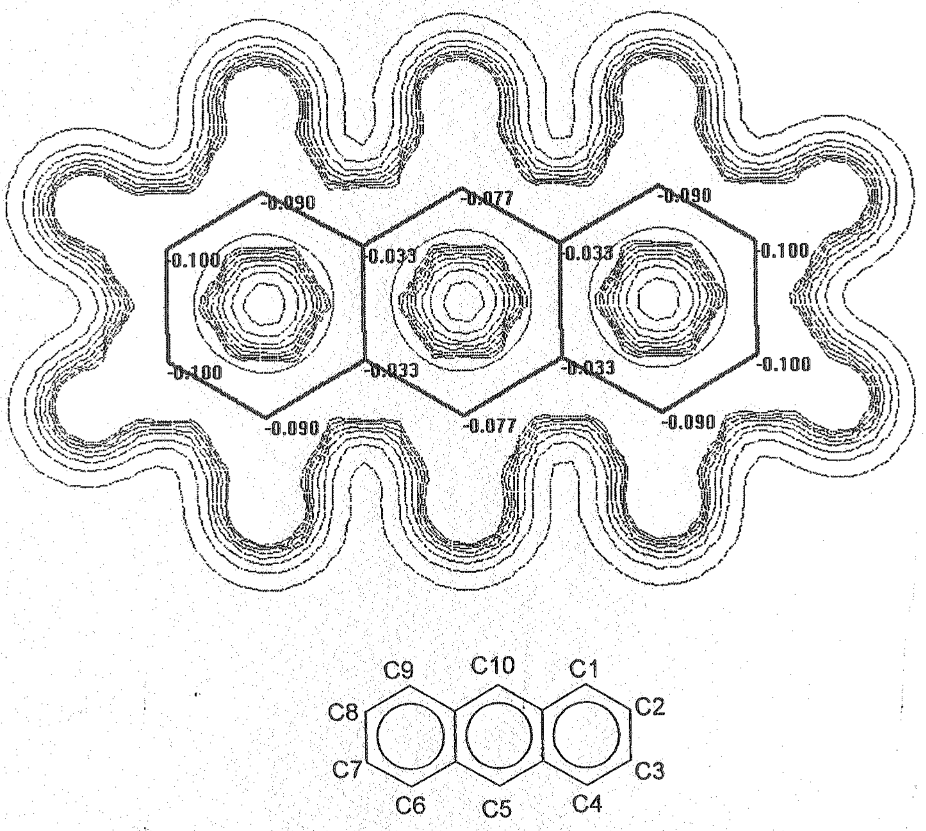

Fig. 2. Charges on and numbering of carbon atoms in anthracene and 2D contour plots of electrostatic potential

It is found that all the carbon atoms in anthracene have slight negative charges with the ones bonded to two carbon atoms being more negative than the ones bonded to three carbon atoms (*e.g.*, C 1 has a negative charge of –0.090 whereas the carbon in between C1 and C10 has a negative charge of –0.033). On the basis of charges it is not possible to explain why the heats of formation of 1,2-epoxide and 2,3-epoxide differ.

The heat of formation of phenanthrene (55.2 kcal mol^{-1}) and that of its 1,2-epoxide (44.5 kcal mol^{-1}) differ only by a small amount whereas there is a large difference between the heats of formation of epoxide and the diol (–42.7 kcal mol^{-1}), meaning that diol formation reaction is more likely to be spontaneous than the epoxide formation reaction. It should be noted that these values as such do not provide any insight as to why phenanthrene is less toxic, generally not considered to be carcinogenic[4] (although it has a bay region). It has been suggested that phenotyping of carcinogenic metabolites would be a more reliable method to determine the role of host metabolism in the PAHs-related cancer[3].

Fig. 3 gives the charges on carbon and hydrogen atoms of 1,3-butadiene along with 2D contour plots for the electrostatic potential. It can be seen that C1 and C4 are slightly more negative than C2 and C3.

Figs. 4–6 give the charges on carbon atoms along with 2D contours for electrostatic potential as applied to benzo(a)pyrene, benzo(a)pyrene-7,8-epoxide and benzo(a)pyrene-7,8-diol-9,10-epoxide, respectively. It can be seen all the carbons of benzo(a)pyrene have slight negative charges with the ones bonded to

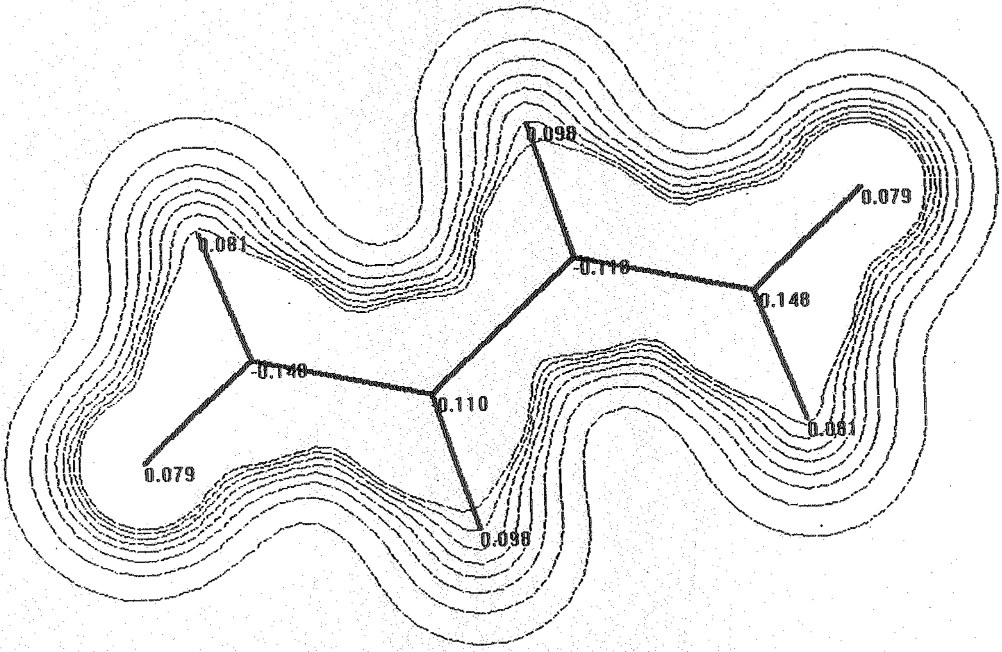

Fig. 3. Charges on atoms of 1,3-butadience and 2D contour plots for electrostatic potential

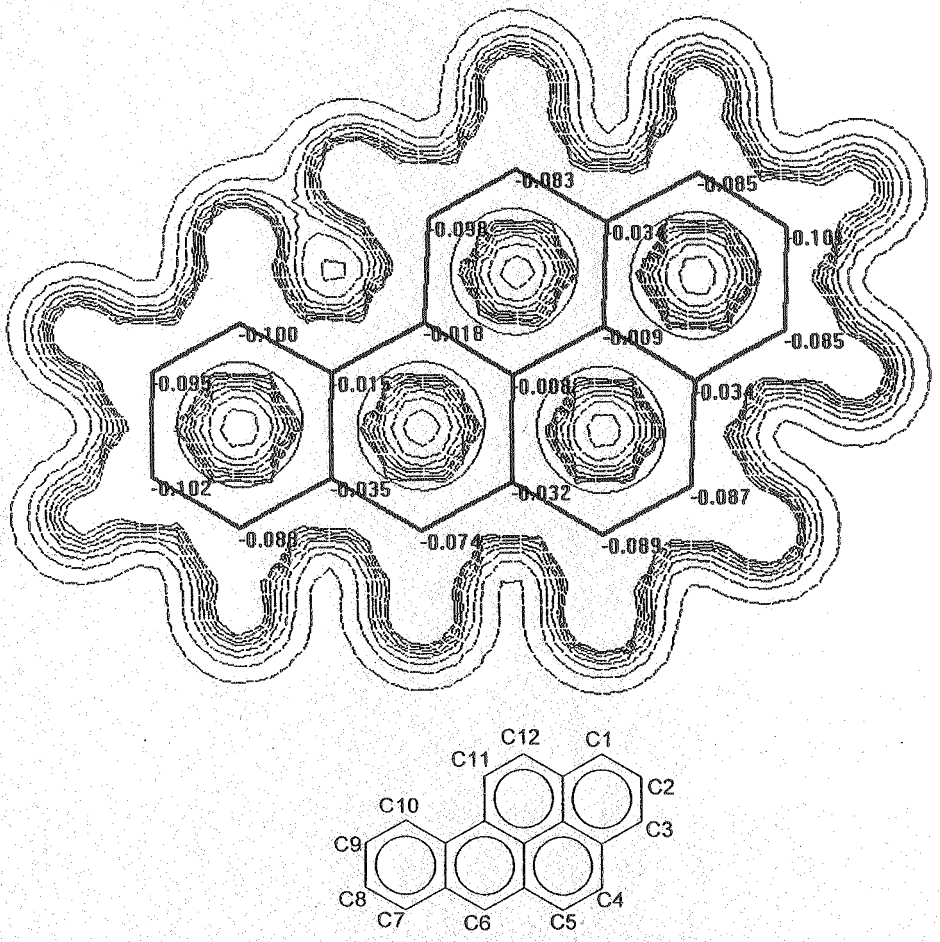

Fig. 4. Charges on and numbering of carbon atoms of benzo(a)pyrene and 2D contour plots for electrostatic potential

two carbons being more negative than the ones bonded to three carbons, as was observed in the case of anthracene. Once again the data do not provide any clue as to why 1,2-epoxide has a lower heat of formation than 7,8-epoxide.

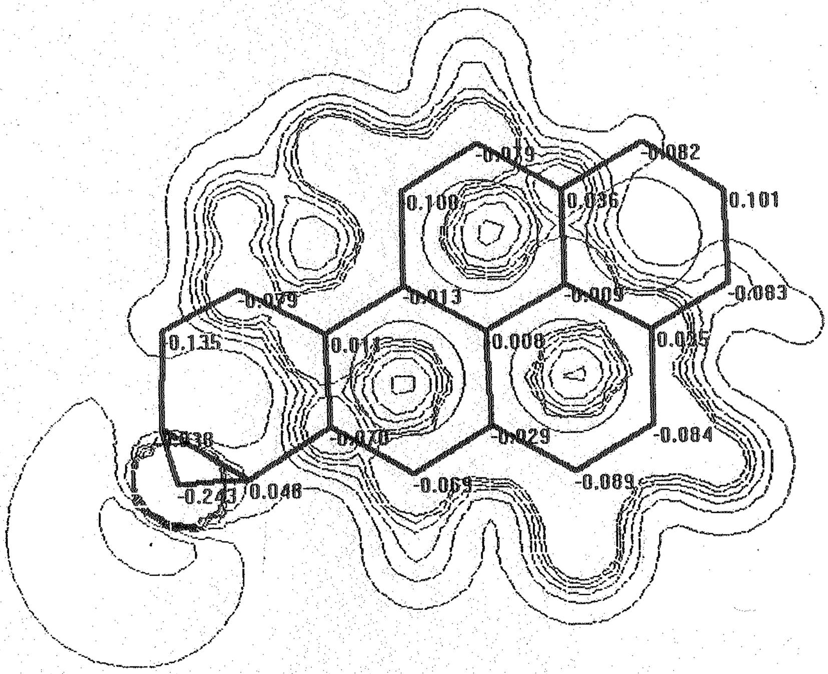

Fig. 5. Charges on and numbering of carbon atoms of benzo(a)pyrene-7,8-epoxide and 2D contour plots for electrostatic potential

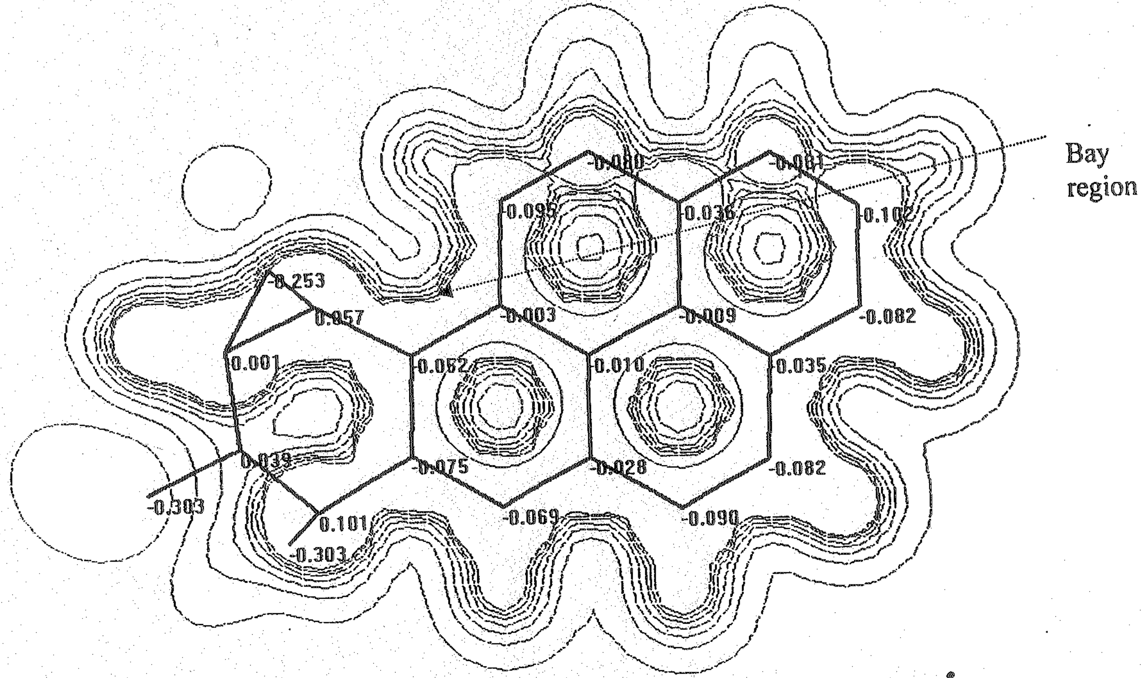

Fig. 6. Charges on carbon atoms and 2D contour plots of electrostatic potential as applied to benzo(a)pyrene-7,8-diol-9,10-epoxide

As expected, epoxide oxygen (which is more electronegative than carbon *i.e.*, has a stronger capacity to compete for the shared electron) has significantly more negative charge on that any of the carbons. In fact, the carbons to which oxygen is bonded each has a slight positive charge.

As stated earlier, benzo(a)pyrene-7,8-diol-9,10-epoxide is an example of bay region diol epoxides which are considered to be the ultimate carcinogenic species of a number of polycyclic aromatic hydrocarbons as they are believed to bind covalently to DNA.

When we compare the electrostatic potential contour plots in the bay region of the benzo(a)pyrene-7,8-epoxide and benzo(a)pyrene-7,8-epoxide-9,10-diol, it can be seen there is a noticeable difference in the plots. The carbons in the bay region have much lower negative charges in benzo(a)pyrene-7,8-epoxide-9,10-diol than in benzo(a)pyrene-7,8-epoxide. For example, C10 in the diol epoxide has a charge of +0.057 whereas in the epoxide it has a charge of –0.079.

Conclusion

Molecular modelling analyses show that the stability of the epoxide formed depends on the position of double bond to which oxygen gets bound giving credence to the idea of site-specificity in metabolic activation.

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