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Theoretical Studies on the Carcinogenic Activity of Diol Epoxide Derivatives of Polycyclic Aromatic Hydrocarbons

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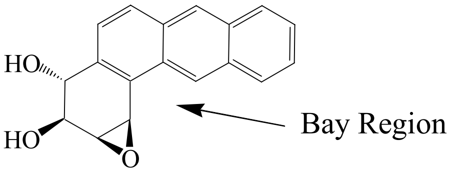
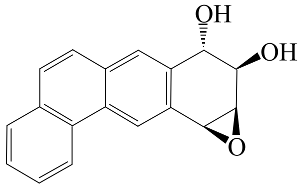
Metabolic activation of a number of polycyclic aromatic hydrocarbons (PAH) leads to the formation of their diol epoxide derivatives.[1] Several experimental evidences demonstrated that a bay-region diol epoxide (bDE) metabolite acts as an ultimate carcinogen.[3-4] Typical example of a bDE is given below (**1**) along with one of its non bay-region diol epoxides **2** (nbDE). Once a bDE is formed, an acid catalyzed reaction would protonate the epoxide oxygen resulting into the opening of the epoxide ring. The carbocation thus formed would react with DNA to form a stable adduct.[2-4] Often the amino groups of adenine and guanine are found to react with the carbocation (cf. Scheme 1). The formation of such stable DNA adducts is considered as the root cause of certain type of cancers. In the present study we will mainly focus on the molecular electrostatic potential (MESP) and electron density features of the bDEs, nbDEs, and their corresponding protonated forms. The geometry optimization and the property calculations have been carried out at B3LYP/6-31G** level of theory.



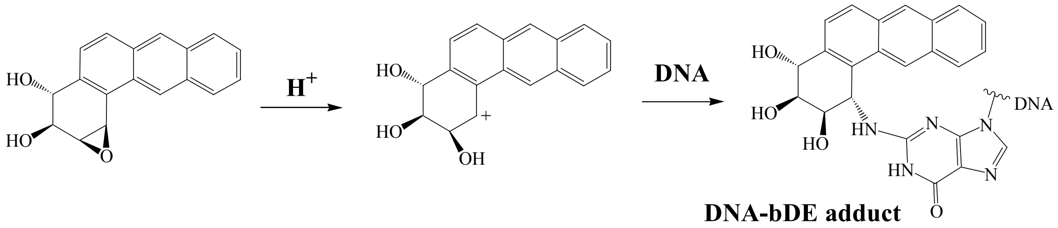
1 Bay region diol epoxide derivative of benzanthracene



2 Nonbay region diol epoxide derivative of benzanthracene

In Figure 2, the MESP features of **1** and **2** are presented. In the case of **1**, the MESP around the aromatic region is similar to anthracene, while that of **2** is similar to phenanthrene. The latter has more electron rich character around the aromatic region as compared to the former, which is in accordance to the higher aromaticity of phenanthrene moiety than the anthracene moiety. The nbDE system **2** is 8.20 kcal/mol more stable than the bDE system **1**, which is in support to the higher aromaticity of **2**. In the case of **1**, the most negative-valued MESP point (a minimum) around the epoxy oxygen is 0.37 kcal/mol more negative than that of **2**. This suggests a slightly higher basicity to the epoxide oxygen of **1** than that of **2**. It is expected that the energetically less stable bDE system **1** containing a more basic epoxy oxygen is more reactive for protonation at the epoxy oxygen as compared to the nbDE system **2**.

In Figure 3, the optimized structures of the protonated forms of **1** and **2** designated respectively as $\mathbf{1H^+}$ and $\mathbf{2H^+}$ are presented along with their LUMO orbital. From the LUMOs of $\mathbf{1H^+}$ and $\mathbf{2H^+}$, it can be assigned that positive charge is almost equally localized on three carbon atoms of $\mathbf{1H^+}$ while in $\mathbf{2H^+}$, it is mainly on the cationic center. This feature can be indirectly visualized from the $\rho(\mathbf{r})$ difference obtained by subtracting the $\rho(\mathbf{r})$ of $\mathbf{1H^+}$ and $\mathbf{2H^+}$ from their corresponding radical forms (**1H** and **2H**) (cf. Figure 4). According to Figure 4, the electron deficient regions of the cationic systems are the regions enclosed in the yellow surfaces. This means that in $\mathbf{1H^+}$ the positive charge is almost equally localized on three carbon atoms while in $\mathbf{2H^+}$, the positive charge is largely centered on the cationic center. Based on these features, it is expected that the life time of **2H**$^+$ could be very short and it can be easily hydrolysed to a tetrol. On the other hand, the life time of **1H**$^+$ could be higher than that of **2H**$^+$ due to the higher charge delocalization in the former and therefore **1H**$^+$ could be a target for a nucleophilic attack by the amino groups of adenine and guanine. The MESP and ρ(**r**) features of other bDE and nbDE systems will also be presented.



Scheme 1. Formation of DNA-bDE adduct

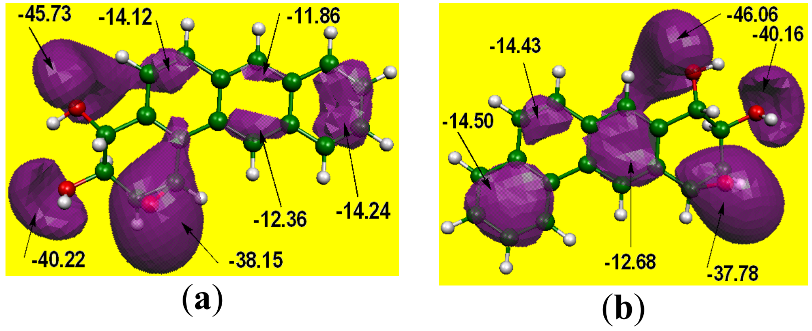


Figure 2. –11.30 kcal/mol valued MESP isosurfaces of (a) **1** and (b) **2**. The value of the most negative valued point in each lob is also depicted.

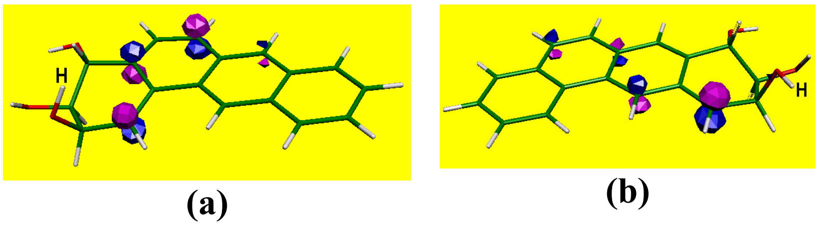


Figure 3. LUMO of (a) **1H**$^+$ and (b) **2H**$^+$.

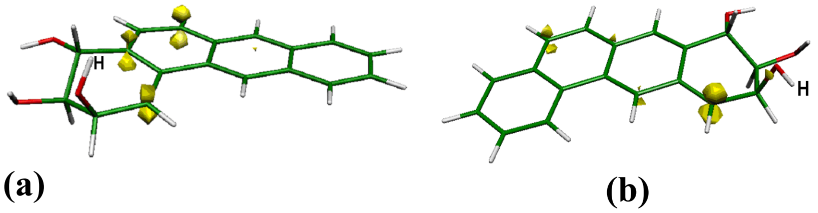


Figure 4. ρ(**r**) difference of value 0.01 a.u. obtained from the cation and the corresponding neutral system. (a) **1H**$^+$ and (b) **2H**$^+$.

References

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