Oxidation and Reduction Process for Polycyclic Aromatic Hydrocarbons and Nitrated Polycyclic Aromatic Hydrocarbons

DISSERTATION

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Epoxidation is the first metabolic activation step necessary for polycyclic aromatic hydrocarbons (PAHs) to exert their biological activity. Nitrated polycyclic aromatic hydrocarbons (NPAHs) may undergo nitro reduction or ring oxidation, or a combination of ring oxidation and nitro reduction. We used density functional theory at the B3LYP/6-31+G**/B3LYP/6-31G* level of theory to explore both the reduction of NPAHs and epoxidation of PAHs and NPAHs. Substituent effects on the stability of nitrobenzene and its derivatives generated in the process of the nitro reduction were investigated. Two linear (free) energy relationships were observed: (1) a correlation between the enthalpy difference $\Delta H_0^{\text{meta}}$ [$\Delta H_0 = H_0(\text{meta}) - H_0(\text{para})$] and the charge differences on the carbon bonded to the reaction site for neutral molecules; and (2) a correlation between the $\Delta H_0^{\text{meta}}$ and the Hammett substituent constant difference $\Delta \sigma$ ($\Delta \sigma = \sigma_m - \sigma_p$). We also explored substituent and solvent effects on the reduction, and linear Hammett correlations were obtained. The effects of ring systems on the reduction thermodynamics were also examined. Larger ring systems and azaheterocycles were found to be generally more feasibly reduced than the parent nitrobenzene system. The thermochemistry of the epoxidation reactions of various PAHs and NPAHs were explored. The regioselectivities of the epoxidations were found to be consistent with the
available experimental data. We also investigated the isomerization process for arene oxides, derived from both PAHs and NPAHs, to form the corresponding oxepines. The calculated results quantitatively demonstrate the facility and the feasibility of the isomerization at room temperature. The results reveal the significant effect of the aromaticity changes on the isomerization. By comparing the results for NPAHs with the results for PAHs, the effect of the nitro group on the isomerization was found to be dependent on the location of the oxirane and the structure of the NPAH. The calculations also reveal that solvation effects on the isomerization of the NPAH oxides are different from and more complex than that of the parent PAH oxides. Our results elucidate the origin of the racemization of the optically active arene oxides.
DEDICATION

Dedicated to my parents, my husband and my daughter
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CHAPTER 1

INTRODUCTION

1.1 Sources of polycyclic aromatic compounds and nitrated polycyclic aromatic compounds.

Polycyclic aromatic hydrocarbons (PAHs) are widely spread environmental pollutants that arise from both natural and human sources. Natural sources include incomplete combustion from the burning of fossil fuels, forest fires, volcanic activity, and \textit{in situ} synthesis from degraded biological materials.\textsuperscript{1,2} Human sources include the burning of coal, coke production, residential fireplaces, coal-fired residential furnaces, automobiles, commercial incinerators, oil-fired commercial boilers and even wear from rubber tires.\textsuperscript{5} The toxicity of tobacco smoke also derives, in part, from PAHs.\textsuperscript{3} PAH emissions are also found during oven broiling, pan-frying and deep-frying food.\textsuperscript{4} Comparing these two sources, human activities are by far the major contributors.\textsuperscript{5}

Similar to PAHs, the nitrated polycyclic aromatic hydrocarbons (NPAHs) can also result from the same sources as for PAHs.\textsuperscript{6-8} In addition, the vast majority of the NPAHs detected in the environment are released from their extensive use in the synthesis of dyes, plasticizers, pesticides, and explosives.\textsuperscript{9} Meanwhile, NPAHs can also be formed by the reactions of parent aromatic compounds, PAHs, with reactive nitrogen-containing
species existing in the atmosphere, such as nitrate (NO$_3$) radical$^{10-20}$ or formed via electrophilic nitration reactions in the presence of NO$_2$.$^{21}$ A number of natural NPAHs are also found from bacterial sources.$^{22}$ Some NPAHs have been isolated from fungi.$^{23}$

Therefore, PAHs and NPAHs exist almost everywhere in our environment. They exist in the atmosphere, in both urban and rural areas, in soil and rocks,$^{24-29}$ in various sediments, fossils, and fossil fuels.$^{1,2}$ They are also spread into aquatic systems from industrial and water treatment plants, seepage, and accidental spills, resulting their existence in rivers, streams, and lakes.$^{30}$ They are even found in our food chain and in tea leaves.$^{3,31,32}$ Some commercial medicines contain PAHs as well. For example, coal tar, a complex mixture of PAHs, is widely used in cream, ointments, lotions, and shampoos for the treatment of psoriasis.$^{33,34}$ With increasing industrial development throughout the world, the production and accumulation rates of PAHs and NPAHs are constantly rising.$^5$

1.2 Toxicity, mutagenicity and carcinogenicity of PAHs and NPAHs

Being ubiquitous in the environment, exposure to PAHs and NPAHs for humans and animals can come from several sources: orally, by inhalation, and through skin contact.$^{35-38}$ Numerous evidence for these compounds’ mutagenic and carcinogenic properties have been approved.$^{28,35,39}$ Combustion products of coal (soot and tars) were the first recognized chemical carcinogens. The early documentation of appearance of scrotal cancer diseases in chimney sweeps was filed in 1775. These cancer diseases have been shown to be caused by PAHs, NPAHs and their azaheterocyclic analogs.$^{38}$ In the 1930s, a carcinogenic PAH, benzo[a]pyrene, was identified in animal studies under controlled conditions.$^{40}$ Following that, further studies that established these compounds’
toxicity, mutagenicity and carcinogenicity have been reported. It is also well established that PAHs and NPAHs play a key role in adverse reproductive outcomes and cardiovascular disease resulting from oxidative and DNA damage.\textsuperscript{38,41-43} Compared with polycyclic aromatic hydrocarbons, the concentrations of nitrated aromatic compounds are much lower,\textsuperscript{44} but many of nitrated polycyclic aromatic hydrocarbons have been found to have higher toxicity than their parent compounds.\textsuperscript{45}

As a result, PAHs, NPAHs and their azaheterocyclic analogs have become an important problem, and as a class of compounds, they endanger human health.

1.3 Mechanism for the toxicity, mutagenicity and carcinogenicity of PAHs and NPAHs

PAHs and NPAHs, a class of well-known environmental pollutants, have long been a hot research topic in many fields, such as organic chemistry, theoretical chemistry, physical chemistry, environmental science, toxicology, cancer research, and energy sciences. A majority of the research has focused on the occurrence, environmental fate, degradation/remediation and chemical transformation. Numerous books and review articles have reported the occurrence and distribution of PAHs and NPAHs in the environment.\textsuperscript{30,35} Meanwhile, their DNA adduct formation, mutagenesis, and carcinogenesis have also been research focuses. And the metabolic activation pathways of PAHs and NPAHs have been studied extensively.\textsuperscript{33,46,47} These environmental pollutants are metabolized by the cellular defense system. This metabolism in a mammalian system is principally carried out in the liver and catalyzed mainly by the cytochrome P450 enzymes along with other metabolizing enzymes.\textsuperscript{30} After metabolism, PAHs and NPAHs become more polar and water-soluble and are excreted out of the body.
to complete the biological “detoxification” process. However, the metabolism of some PAHs and NPAHs also generates reactive intermediates that are capable of forming covalent adducts with DNA or other biological substances, leading to toxicity, mutagenicity and carcinogenicity. Generally, PAHs and NPAHs are highly stable, both chemically and physically, and are resistant to biological degradation. Therefore, these compounds require metabolic activation in order to exert their adverse effects.

For PAHs, it is generally accepted that formation of diol-epoxide-derived DNA adducts is the principal mammalian metabolic activation pathway leading to cancer initiation (Scheme 1.1). The biological oxidation of PAHs is first catalyzed by the cytochrome P-450 monooxygenases to produce epoxides, followed by epoxide hydrase enzyme-mediated hydrolysis to the trans diols, and then a second epoxidation at the adjacent double bond. This metabolic process yields a diol-epoxide, 7,8-dihydrodiol-9,10-epoxide, which reacts with nucleophilic DNA, represented in this scheme as guanosine. The diol-epoxide-derived DNA adducts can initiate a multistage process leading to genetic effects, including cancer, cardiovascular damage, and adverse reproductive outcomes. Some diol-epoxide-derived DNA adducts have been identified from metabolism of a number of PAHs and NPAHs in vitro and in vivo, and their structures have been well characterized. Evidence to support this theory has been growing since 1968 when Jerina et al. isolated naphthalene-1,2-oxide, an intermediate, as a metabolite of naphthalene. The produced electrophilic reactive products (e.g., epoxides, diol-epoxides) can also react with other nucleophiles in the cell (e.g., proteins) and thus cause toxicity.
Scheme 1.1. Metabolically activated pathways of benzo[a]pyrene leading to the formation of diol-epoxide-derived DNA adducts.

The carcinogenesis of NPAHs has been intensively studied since the early 1980s. The metabolic activation pathways as shown in Scheme 1.2, are more complicated than their parent compounds due to the presence of the nitro group. In addition to ring oxidation, nitrated aromatic compounds may undergo nitro reduction, or a combination of ring oxidation and nitro reduction. In the nitro-reduction pathway, the nitro group is reduced to a nitroso functionality, then to a hydroxylamine, and subsequently to a substituted nitrenium ion. Nitrenium ions are highly reactive electrophiles that can add to DNA to form covalent DNA adducts, resulting in their biological toxicity, mutagenicity, or carcinogenicity.
Scheme 1.2. Metabolically activated pathways of 1-nitro-benzo[a]pyrene leading to the formation of DNA adducts and the subsequent induction of mutation in CHO cells, as proposed by Zhan et al.\textsuperscript{54}

1.4 The effects of the molecular structure of PAHs and NPAHs on their toxicity, mutagenicity and carcinogenicity

Although structures of PAHs and NPAHs are very homogeneous, their carcinogenic effect can be classified into four different categories according to their power: inactive, slight, moderate and high. A great effort was made in scientific research
to connect the molecular structure to its eventual toxic effect. Compound structure, position of substitution, and presence of heteroatoms in the ring have all been found to affect the carcinogenic and/or mutagenic properties of these aromatic compounds.\textsuperscript{5}

The K-L-M-“bay region” theory was provided to explain the carcinogenicity of many PAHs. Figure 1.1 shows a graphical example of these general regions for a particular PAH.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure1.png}
\caption{The K-, L-, M- and bay-region of benzo[a]anthracene.}
\end{figure}

In 1931, Schmidt suggested that PAHs with high \(\pi\)-electron density in the L-region are strongly carcinogenic.\textsuperscript{60} Contrary to this, in 1955, Pullman and Pullman pointed out that high \(\pi\)-electron density exists in the K-region while low density is in the L-region; therefore, the high electron-density in the K-region was correlated to a high level of carcinogenicity.\textsuperscript{61,62} Later, Gayoso and Kimri suggested that the M region could replace the K region for an improvement of the structure-carcinogenic activity relationships.\textsuperscript{63,64}
Until in 1977, Jerina employed Perturbational molecular-orbital calculation and found that epoxides on saturated benzo ring that form part of the “bay region” of a PAH undergo ring opening to a carbonium ion (Scheme 1.3) much more easily than the non-bay-region epoxides. These unique electronic properties result in that the “bay region” diol epoxides are highly reactive and susceptible to attack by nucleophiles, such as DNA and thus become the main factor responsible for the toxic action.65-68

![Scheme 1.3 Ring opening of a “bay region” diol epoxides to a carbonium ion.](image)

Based on this “bay region” theory, many studies have been carried out trying establish quantitative structure-activity relationships using different empirical and theoretical methods.69-78 Since most of the data for the biological activities are from animal studies,78b it is reasonable to argue whether data on animal metabolism is relevant to humans along with the established structure-activity relationship.

As mentioned above, NPAHs are metabolized by either reductive or oxidative pathways or both as shown in Scheme 1.2 for 1-nitro-benzo[a]pyrene as an example.
These NPAHs exhibit different carcinogenicity from their parent PAHs. This toxicity is also highly variable between regioisomers.\textsuperscript{43,79} Nitro orientation was found to be an important structural feature that affects metabolism, DNA binding, toxicity, mutagenicity and carcinogenicity of NPAHs.\textsuperscript{43,76,80} This conclusion is based on the results of more than 40 NPAHs, which have been tested for the effects of the orientation of the nitro group on their toxicity.\textsuperscript{76-78} A general finding is that NPAHs with the nitro substituent oriented perpendicular to the aromatic system exhibit either very weak or no direct-acting mutagenicity in \textit{S. typhimurium} strains TA98 and TA100.\textsuperscript{43} Fu \textit{et al.} proposed that when a nitro group is introduced to a carcinogenic bay-region containing PAH, the nitro group preferentially adopts a perpendicular or nearly perpendicular orientation and the toxicity of this NPAHs is weaker than the parent PAH.\textsuperscript{30,81} To our best knowledge, there is no quantitative structure-activity relationships have been established due to the complexity of NPAH structures and metabolism.

These studies have enriched our understanding on the relationship between biological activities of PAHs and NPAHs with their electronic and structural properties. But in order to more accurately predict the biological activities, such as toxicity, mutagenicity and carcinogenicity, of NPAHs and PAHs, more studies are needed, especially the studies on reactions occurring during their metabolic activation process.

1.5 \textit{Scope of our research}

The above research focuses on the effects of the molecular structure of PAHs and NPAHs on their biological activities provide us useful information. In order to understand qualitatively, and ideally also quantitatively, the chemical origins of their
biological activities, detailed information regarding quantitative energetic changes during their biological transformations has to be obtained at a molecular level. This philosophy leads us to focus on the activation pathways shown in Schemes 1.1 and 1.2.

One of the activation pathways of NPAHs is the nitro-reduction pathway (shown in Scheme 1.2). The reduction of nitroaromatic compounds has been explored by using both biological studies and synthetic studies.\textsuperscript{45,56,82-84} These studies have produced two important findings relevant to the present study.\textsuperscript{45} First, the bioactivities of nitroaromatic compounds, such as toxicity, mutagenicity, and carcinogenicity, are highly correlated to the ease of reduction of the arene; further, the ease of reduction of the aromatic nitro group depends on the nature of the aromatic rings, the substituents attached to the ring, and the solvent environment. The second important finding is that the high reactivity of the nitroso and hydroxylamino intermediate is responsible for much of the toxicity and carcinogenicity attributed to nitroaromatic compounds. Because many intermediates generated in the reduction process are too chemically active or unstable to detect,\textsuperscript{45} and the existence of regioisomeric forms of nitroarenes complicates both the analysis and the identification, it is difficult to experimentally study these reactions. To our knowledge, no experimental studies to date have comprehensively examined the reduction, including effects of substituents, the role of solvation, effects of different arene ring systems and the position of the nitro group on the reduction thermodynamics. Therefore, computational methods constitute an important tool. In order to comprehensively understand the reduction of nitrated aromatic compounds and to determine the principal factors that cause their toxicity, mutagenicity and carcinogenicity, an extensive
computational investigation of these pathways has been carried out and is discussed in Chapter 2.

In the oxidative pathway of both PAHs and NPAHs shown in Schemes 1.1 and 1.2, respectively, the diol-epoxide derivatives exhibit different biological activities, depending on their location within a given PAH or NPAH; generally, the bay-region derivatives exhibit higher mutagenic and carcinogenic activity.\(^{85}\) This theory illustrates the importance of predicting the regioselectivity of the first-step epoxidation, since it largely determines what diol-epoxide will be subsequently generated. Due to the instability of these epoxides and the resulting challenges in their preparation and characterization, not to mention the challenges in separation and identification of regioisomeric forms of nitroarenes, experimentally studying the epoxidation is extremely difficult. Consequently, a computational approach (at the B3LYP/6-31+G**/B3LYP/6-31G* level of theory) to understand the origin of the regioselectivity of the epoxidation (first step shown in Scheme 1) of PAHs is discussed in Chapter 3. In Chapter 4, a comprehensive computational examination on the epoxidation regioselectivities, the effects of the nitro group and solvation on the regioselectivities, and epoxidation preferences for NPAHs relative to unsubstituted PAHs has been completed, and the results will be discussed.

In the process of the epoxidation of PAHs and NPAHs shown in Schemes 1.1 and 1.2, respectively, the oxygen atom is preferentially added to one stereoheterotopic face of an aromatic ring by the monooxygenase enzyme to form the optically active arene oxides.\(^{86}\) The subsequent enzyme-catalyzed reactions and biological activities of arene oxides are often dependent upon their absolute configuration. The initial epoxide (arene
oxide) intermediates in biological systems are generally difficult to detect due to their propensity for side reactions (aromatization via formation of the corresponding phenols and facile ring-opening by various electrophiles in biological systems). In order to investigate the absolute configuration of arene oxides and their further reactions, several asymmetric syntheses of arene oxides have been developed. Studies on arene oxides derived from single enantiomer precursors have shown that their configurational stabilities vary with the structures of the PAHs. Some arene oxide enantiomers spontaneously racemize, while other arene oxides, such as phenanthrene-1,2-oxide and 3,4-oxide, were initially obtained in enantiopure form, but were observed to racemize slowly at ambient temperature via undetected oxepine isomers. Some arene oxides are very stable in their optical activity, such as anthracene-1,2-oxide and naphthalene-1,2-oxide. The racemization of enantiopure arene oxides results from the oxirane ring inversion between the two faces of the arene via an oxepine isomer as shown in Scheme 1.3.

![Scheme 1.4](image)

**Scheme 1.4.** The most plausible mechanism for the racemization of arene oxides.
First, the oxirane ring is opened to give the corresponding oxepine, then recloses to give either enantiomer of the arene oxide, resulting in racemization. However, many of the oxepine intermediates and epoxides derived from PAHs are unstable, so this scheme may be difficult to verify experimentally. In Chapter 5, a comprehensive computational examination of the feasibility and facility of the isomerization of arene oxides on energetic grounds, and an investigation on the effects of structural changes and solvent changes on the energetics of the isomerization are discussed. A computational study on the isomerization of epoxides derived from NPAHs is discussed in Chapter 6 using both thermodynamic and kinetic arguments. In Chapter 6, the effects of nitro group, solvation and structural changes on the isomerization are also discussed.

1.6 References


CHAPTER 2

COMPUTATIONAL STUDY OF THE REDUCTION OF SUBSTITUTED NITROBENZENE, NITRATED PAH AND NITRATED AROMATIC AZAHETEROCYCLES

2.1 Introduction

Incomplete combustion processes, such as those occurring in diesel engines, lead to the generation of polycyclic aromatic hydrocarbons (PAHs) and their nitrated derivatives in the environment. Nitrated aromatic compounds can also be formed by the reactions of parent aromatic compounds with reactive nitrogen-containing species existing in the atmosphere.\(^1\)\(^-\)\(^9\) A number of natural nitrated aromatic compounds are also found from bacterial sources,\(^10\) and some nitrated aromatic compounds have been isolated from fungal sources.\(^11\) Nitrated aromatic compounds are widespread in both urban and rural areas, in the air, soil and rocks.\(^12\)\(^-\)\(^17\) Although the concentrations of nitrated aromatic compounds are lower than those of their parent aromatic compounds,\(^18\) some of them have been found to have more potent toxicity than their parent compounds.\(^10\),\(^19\)

Both PAH and their nitrated derivatives generally exert their biological activity through metabolic activation, which produces reactive intermediates which can react with
biological molecules, especially DNA.\textsuperscript{20,21} Scheme 2.1 shows example metabolic activation pathways of a nitrated aromatic compound leading to the formation of DNA adducts and the subsequent induction of mutation in CHO cells, as suggested by Zhan \textit{et al.}\textsuperscript{22} The presence of the nitro group makes the metabolism of nitrated aromatic compounds more complicated than the parent compounds: in addition to ring oxidation, nitrated aromatic compounds may undergo nitro reduction, or a combination of ring oxidation and nitro reduction.\textsuperscript{22} In the nitro-reduction pathway, the nitro group is reduced to a nitroso functionality, then to a hydroxylamine, and subsequently to a substituted nitrenium ion. Nitrenium ions are highly reactive electrophiles that can add to DNA to form covalent DNA adducts, resulting in their biological toxicity, mutagenicity, or carcinogenicity.\textsuperscript{1,22-24} Consequently, this class of compounds has attracted increasing attention in recent years, and the transformations and the biological activities of nitroaromatic compounds has been extensively studied. The reduction mechanism of nitroaromatic compounds has been explored by using both biological studies and synthetic studies for a long time.\textsuperscript{23-27}
Scheme 2.1. Metabolically activated pathways of 1-nitro-benzo[a]pyrene leading to the formation of DNA adducts and the subsequent induction of mutation in CHO cells, as proposed by Zhan et al.\textsuperscript{22}

With NPAHs, either one-electron or two-electron reduction mechanisms have been suggested to operate depending on the reaction conditions (Scheme 2.2).\textsuperscript{24} The one-electron reduction of the nitro group initially produces the nitrated radical anion. Enzymes from a variety of sources, including strictly anaerobic bacterial as well as plants and animals, catalyze this one-electron reduction of the nitro group.\textsuperscript{24,26} In the two-electron mechanism, reduction of the nitro group is carried out through sequential
addition of pairs of electrons, and thus no radicals are produced. Nitroreductases convert nitro groups into nitroso intermediates and then to either hydroxylamines or amines by the addition of electron pairs donated by reduced pyridine nucleotides.\(^{24}\)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{R} & \quad \text{R} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{R} & \quad \text{R} \\
\end{align*}
\]

\[\text{1e} \quad \text{1e} / \text{H}^+ \quad \text{1e} / \text{H}^+ \]

\[\text{2e} / \text{2H}^+ \quad \text{2e} / \text{2H}^+ \quad \text{2e} / \text{H}^+ \]

\[\text{O}_2 \quad \text{O}_2 \quad \text{O}_2 \]

\[\text{- OH} \quad \text{-OH} \quad \text{- OH} \]

Scheme 2.2. Reduction of nitro groups by one-electron and two-electron mechanisms.\(^{24}\)

Studies of nitroarenes have produced two important findings relevant to the present study.\(^{24}\) First, the ease of reduction of the aromatic nitro group depends on the nature of the aromatic rings, the substituents attached to the ring, and the solvent environment. The bioactivities of nitroaromatic compounds, such as toxicity, mutagenicity, and carcinogenicity, are highly correlated to the ease of reduction of the arene. The second important finding is that the high reactivity of the nitroso and hydroxylamino intermediate is responsible for much of the toxicity and carcinogenicity attributed to nitroaromatic compounds. Therefore, in order to comprehensively understand the reduction of nitrated aromatic compounds and to determine the principal factors that cause their toxicity, mutagenicity, or carcinogenicity, exploring substituent
effects, the role of solvation, and effects of large aromatic ring systems on the reduction is very important. However, to our knowledge, no experimental studies to date have comprehensively examined the effects of substituents, the role of solvation, the effects of different arene ring systems and the position of the nitro group on the reduction’s thermodynamics. Of course, there are many technical challenges in studying these reductions experimentally. For example, many intermediates generated in the reduction process are too chemically active or unstable to detect. Additionally, the existence of regioisomeric forms of nitroarenes complicates both the analysis and the identification. In this vein, a computational investigation of these pathways can be particularly informative. Several theoretical studies related to nitroarenes have been reported. However, to our knowledge, this is the first systematic and comprehensive computational study that has been performed for the reduction of nitroarenes.

Herein, we report substituent effects on the stability of the reference compound nitrobenzene and the reactive species generated in the process of the reductions as computed with density functional theory (B3LYP/6-31+G**//B3LYP/6-31G*). Subsequently, the effects of solvation and larger nitrated ring systems and nitrated azaheterocyclic analogs on the reductions were explored, and the results for the larger nitrated ring systems and nitrated azaheterocyclic analogs were compared with the reduction of the parent nitrobenzene system.
2.2 Computational Methods

Scheme 2.3 shows the reduction process. We elected to employ molecular hydrogen as a reductant and a one-electron mechanism as an operant mechanism for these studies. Since we are concerned here with the thermodynamics of these reactions, and since all of the thermodynamic energies are relative, the nature of the reductant and the mechanisms from Scheme 2.3 will not affect the overall conclusions of our study.
Overall reaction:

\[
\text{NO}_2^- + 3\text{H}_2 \rightarrow \text{NH}_2^+ + \text{H}_2\text{O}
\]

\[R = \text{Me, OMe, F, Cl, Br, CONH}_2, \text{NO}_2, \text{CHO, CN and H at } meta-, ortho- \text{ and } para-\text{position}\]

**Scheme 2.3.** Reduction process from substituted nitrobenzene to aniline for a one-electron, stepwise mechanism.
Hybrid density functional theory (DFT) was employed to obtain optimized geometries and vibrational frequencies for all stationary points at the B3LYP/6-31G* level of theory. Single-point energies were obtained at the B3LYP/6-31+G** level based on the optimized B3LYP/6-31G* geometries. The effect of solvation was investigated with the polarizable continuum model (PCM) for water and benzene using single-point energy calculations at the B3LYP/6-31+G** level and using the gas-phase optimized geometries. All calculations were performed with Gaussian 03.

All reactants and products were confirmed to be energetic minima via vibrational frequency analyses at the B3LYP/6-31G* level of theory. Scaling factors of 0.9806 were used for the zero-point vibrational energy (ZPE) corrections for the B3LYP/6-31G* geometries. Enthalpies and free energies at 298 K ($H_{298}$ and $G_{298}$, respectively) were obtained from the calculated thermal and entropic correction using the unscaled vibrational frequencies. Enthalpies at 0 K ($H_0$) were calculated from single-point energies and scaled zero-point energies. Since the enthalpies ($\Delta H_{298}$) and the free energies ($\Delta G_{298}$) of reaction at 298 K have the same trends as the enthalpies of reaction at 0 K ($\Delta H_0$), for convenience in the discussion, only $\Delta H_0$ values are discussed; however, the $\Delta H_{298}$ and $\Delta G_{298}$ values are provided in the supporting information. Atomic charges and spin densities were calculated at the B3LYP/6-31+G**//B3LYP/6-31G* level of theory using the natural population analysis method.

The stabilities of meta- and ortho-substituted isomers relative to the para-substituted isomers were computed as the relative enthalpies at 0 K in the gas phase between the energies of the different isomers:
\[ \Delta H_0^{\text{meta}} = H_0(\text{meta}) - H_0(\text{para}) \quad (1) \]
\[ \Delta H_0^{\text{ortho}} = H_0(\text{ortho}) - H_0(\text{para}) \quad (2) \]

The sensitivity of the reduction to the substituents at the meta- or para-position was measured through linear Hammett correlations and reaction constants (\(\rho\)):\(^{39}\) plotting the value of \(\Delta (\Delta H_0)\), which is the difference between the \(\Delta H_0\) of the reduction when the substituent \(R = H\) and the \(\Delta H_0\) when \(R \neq H\), versus \(\sigma\) of the corresponding substituents; the slope of the obtained straight line is the reaction constant \(\rho\).

### 2.3 Results and Discussion

#### 2.3.1 Substituent effects on the stabilities of nitrobenzene and its reduction intermediates

We explored a wide variety of substituents on the thermodynamics of these reduction processes, including both ortho-para-directing substituents (such as OMe, F, Cl, Br and Me group) and meta-directing substituents (such as CN, NO\(_2\), CHO and CONH\(_2\) group). The effects of these substituents on the energies of nitrobenzene as well as on the energies of the intermediates generated during the reduction were considered. The total reduction of a nitro group to an amino group requires seven steps. As shown in Scheme 2.3 for this reduction process, some of the intermediates are neutral compounds, some are radicals and some are radical anions.

All of the relative enthalpies \(\Delta H_0^{\text{meta}}\) and \(\Delta H_0^{\text{ortho}}\) of the meta- and ortho-substituted nitrobenzene derivatives, respectively, relative to their para-substituted regioisomer in the gas phase were calculated according to equations (1) and (2), and the values are listed in Table 2.1. Positive values of \(\Delta H_0^{\text{meta}}\) and \(\Delta H_0^{\text{ortho}}\) indicate that the substance is computed to be less stable than the corresponding para-isomer; conversely,
negative $\Delta H_0^{\text{meta}}$ and $\Delta H_0^{\text{ortho}}$ values indicate that the substance is computed to be more stable than the \textit{para}-substituted compound. Furthermore, the magnitudes of $\Delta H_0^{\text{meta}}$ and $\Delta H_0^{\text{ortho}}$ reflect any differences in stability. From Table 2.1, most of the \textit{ortho}-substituted nitroarenes are less stable than their \textit{para}- and \textit{meta}-substituted isomers. This result can be readily explained by a significant steric effect when \( R = \text{Me, CONH}_2, \text{CHO and NO}_2 \) for which steric crowding leads to added electronic repulsion. For example, as shown in Figure 2.1, both nitro groups in 1,4-dinitrobenzene and 1,3-dinitrobenzene are nearly coplanar with the benzene ring; conversely, 1,2-dinitrobenzene shows twisting of the nitro groups out of the plane of the aromatic ring as the C–C–N–O dihedral angle is $-37.9^\circ$. Consequently, this \textit{ortho}-substituted isomer is higher in energy than the \textit{para}- or \textit{meta}-substituted isomers.

\[
\begin{align*}
\tau_{\text{C–C–N–O}} &= 0.0^\circ \\
\tau_{\text{C–C–N–O}} &= -37.9^\circ \\
\tau_{\text{C–C–N–O}} &= 0.0^\circ
\end{align*}
\]

\hspace{1cm} 1,4-dinitrobenzene \hspace{1cm} 1,2-dinitrobenzene \hspace{1cm} 1,3-dinitrobenzene

\textbf{Figure 2.1.} The structures of the three regioisomeric dinitrobenzene with their C–C–N–O dihedral angles ($\tau$), as optimized at the B3LYP/6-31G* level of theory.

For \( R = \text{OMe, F, Cl, Br and CN} \) substituents, the destabilization of the \textit{ortho}-substituted isomer can be attributed to Coulombic repulsion, as shown in Figure 2.2 for \textit{o-}
methoxynitrobenzene and \( o \)-bromo(hydroxylamino)benzene. For \( o \)-methoxynitrobenzene, the two electronegative oxygen atoms are forced into close proximity. Moreover, two positively charged carbons in the ring are bonded to each other. For \( o \)-bromo(hydroxylamino)benzene, one of the hydrogen atoms from the hydroxylamino group is positive charged (+0.407) and it is close to the positively charged bromine atom.

**Figure 2.2.** The structures of \( o \)-methoxynitrobenzene (left) and \( o \)-bromo(hydroxylamino)benzene (right) with NPA atomic charges provided for selected atoms, as calculated at the B3LYP/6-31+G**/B3LYP/6-31G* level of theory.
<table>
<thead>
<tr>
<th>R (σ_p, σ_m)^a</th>
<th>nitrobenzene</th>
<th>radical anion</th>
<th>radical</th>
<th>nitroso</th>
<th>nitroso radical anion</th>
<th>hydroxylamine radical</th>
<th>hydroxylamine</th>
<th>amine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>meta</td>
<td>ortho</td>
<td>meta</td>
<td>ortho</td>
<td>meta</td>
<td>ortho</td>
<td>meta</td>
<td>ortho</td>
</tr>
<tr>
<td>OMe (-0.27; 0.12)</td>
<td>2.07</td>
<td>7.89</td>
<td>-3.55</td>
<td>5.75</td>
<td>-0.50</td>
<td>6.42</td>
<td>1.66</td>
<td>4.94</td>
</tr>
<tr>
<td>Me (-0.17; -0.07)</td>
<td>0.46</td>
<td>3.18</td>
<td>-0.76</td>
<td>3.42</td>
<td>-0.10</td>
<td>2.82</td>
<td>0.55</td>
<td>1.29</td>
</tr>
<tr>
<td>F (0.06; 0.34)</td>
<td>1.07</td>
<td>7.25</td>
<td>-2.16</td>
<td>7.47</td>
<td>-0.17</td>
<td>6.07</td>
<td>1.09</td>
<td>4.34</td>
</tr>
<tr>
<td>Cl (0.23; 0.37)</td>
<td>0.83</td>
<td>7.87</td>
<td>-0.27</td>
<td>10.50</td>
<td>0.35</td>
<td>7.60</td>
<td>0.77</td>
<td>3.81</td>
</tr>
<tr>
<td>Br (0.23; 0.39)</td>
<td>0.55</td>
<td>7.24</td>
<td>-0.11</td>
<td>9.54</td>
<td>0.24</td>
<td>6.80</td>
<td>0.36</td>
<td>2.83</td>
</tr>
<tr>
<td>CN (0.66; 0.56)</td>
<td>0.27</td>
<td>5.38</td>
<td>5.14</td>
<td>8.76</td>
<td>1.32</td>
<td>5.27</td>
<td>0.14</td>
<td>2.45</td>
</tr>
<tr>
<td>NO_2 (0.78; 0.71)</td>
<td>-0.08</td>
<td>10.04</td>
<td>9.66</td>
<td>19.83</td>
<td>1.70</td>
<td>10.28</td>
<td>-0.39</td>
<td>7.51</td>
</tr>
<tr>
<td>CHO</td>
<td>-0.58</td>
<td>5.13</td>
<td>6.72</td>
<td>8.65</td>
<td>1.43</td>
<td>4.04</td>
<td>-0.61</td>
<td>2.21</td>
</tr>
<tr>
<td>CONH_2</td>
<td>-0.64</td>
<td>5.92</td>
<td>4.20</td>
<td>4.41</td>
<td>0.55</td>
<td>4.48</td>
<td>-0.81</td>
<td>-0.85</td>
</tr>
</tbody>
</table>

^a σ_p is the substituent constant for the para-position and σ_m is the substituent constant for the meta-position.

^b The substituent constants for the para- and the meta-positions were not available.

**Table 2.1.** Gas-phase enthalpies (ΔH_{meta} and ΔH_{ortho}, kcal/mol) of meta- and ortho-substituted nitrobenzene derivatives, as shown in Scheme 2.3, relative to their para-substituted regioisomers (B3LYP/6-31+G**// B3LYP/6-31G*).
In a few cases, \textit{ortho}-substituted isomers were found to be lower in energy than the \textit{meta}- or \textit{para}-substituted isomers. In these cases, the adjacent substituents have the capability of forming intramolecular hydrogen bonds, or attractive charge-charge interactions. For example, as shown in Figure 2.3 for \textit{o}-methoxyaniline and \textit{o}- (aminocarbonyl)nitrosobenzene radical anion, respectively, the \textit{ortho}-substituted isomers are stabilized due to intramolecular hydrogen bonding. When this attractive interaction is stronger than the steric effect, the \textit{ortho}-substituted isomers are more stable than their \textit{para}-substituted isomers. In some cases, these \textit{ortho}-substituted nitroarenes are even more stable than their \textit{meta}-substituted isomers; for example, the relative $\Delta H_0$ enthalpies are $-2.29$, $-2.15$, $3.94$, and $-4.74$ kcal/mol for \textit{m}-methoxyaniline, \textit{o}-methoxyaniline, \textit{m}- (amido)nitrosobenzene radical anion and \textit{o}- (amido)nitrosobenzene radical anion, respectively.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structure.png}
\caption{The structures of \textit{o}-methoxyaniline (left) and \textit{o}- (aminocarbonyl)nitrosobenzene radical anion (right) with NPA atomic charges provided for selected atoms, as calculated at the B3LYP/6-31+G**//B3LYP/6-31G* level of theory.}
\end{figure}

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When comparing the *meta*-substituted compounds with their *para*-substituted isomers (Table 2.1), no clear-cut relationship between the site of substitution and the relative enthalpy is evident. Obviously, the nature of the substituent as well as the site of substitution affects the reaction enthalpy. For some substituents, the *meta*-substituted isomers are more stable than the *para*-substituted isomers ($\Delta H_{0}^{\text{meta}} < 0$); while for other substituents, the *para*-substituted isomers are more stable ($\Delta H_{0}^{\text{meta}} > 0$). Moreover, the substituent effects show no evident trends for the different reduction intermediates.

In order to provide a more sophisticated analysis of the substituent effects on the stabilities of these substances, the atomic spin densities (populations) and charges were computed using a natural population analysis (NPA) partitioning scheme. By plotting the $\Delta H_{0}^{\text{meta}}$ (eq 1) values against the charge differences on the carbon bonded to the reaction group (nitro, nitroso, hydroxylamino, and amino), a linear relationship was found for neutral nitroarenes and the neutral reduction intermediates. The linear relationships with the corresponding squared correlation coefficient ($R^2$) are listed in Table 2.2. As shown in Table 2.2, the positive slopes between 23.8 to 29.5, and the small, positive intercepts on $\Delta H_{0}^{\text{meta}}$ (0.42 to 0.51) suggest that the stabilities of these compounds are directly correlated to the charge density on the carbon bonded to the reaction site. A more positive charge on the carbon adjacent to the reaction site is correlated with a more unstable structure. When the charge difference is zero, the *para*-substituted compounds are slightly more stable than the *meta*-substituted isomers.
 Relationship \( \Delta H_0 = \)  

<table>
<thead>
<tr>
<th>substances</th>
<th>nitro</th>
<th>nitroso</th>
<th>hydroxylamine</th>
<th>amine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relationship ( \Delta H_0 = )</td>
<td>(28.5x + 0.42)</td>
<td>(29.5x + 0.44)</td>
<td>(27.0x + 0.42)</td>
<td>(23.8x + 0.51)</td>
</tr>
<tr>
<td>(R^2)</td>
<td>0.86</td>
<td>0.81</td>
<td>0.80</td>
<td>0.79</td>
</tr>
</tbody>
</table>

\(a\) All of the enthalpies are calculated at the B3LYP/6-31+G**//B3LYP/6-31G* level of theory.  
\(b\) Each function was obtained from a graph of \(\Delta H_0^{\text{meta}}\) vs charge difference \(x\).

**Table 2.2.** The linear relationships between the \(\Delta H_0^{\text{meta}}\) (eq 1) and the charge differences (\(x\)) on the carbon bonded to the reaction site and the corresponding correlation coefficient \(R^2\). \(a\)

Another important linear relationship between the \(\Delta H_0^{\text{meta}}\) and the \(\Delta \sigma (\Delta \sigma = \sigma_m - \sigma_p)\) \(^{40}\) was found for all of the \(meta\)-substituted nitrobenzene and their derivatives, including neutral molecules, radicals and radical anions. These relationships with the corresponding correlation coefficients are listed in Table 2.3.

<table>
<thead>
<tr>
<th>substances</th>
<th>Nitro benzene</th>
<th>radical anion</th>
<th>radical</th>
<th>nitroso radical anion</th>
<th>Hydroxylamine radical</th>
<th>Hydroxylamine</th>
<th>amine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relationship ( \Delta H_0^{\text{meta}} = )</td>
<td>(3.7\Delta \sigma + 0.3)</td>
<td>(-22.7\Delta \sigma + 3.8)</td>
<td>(-4.3\Delta \sigma + 0.95)</td>
<td>(3.6\Delta \sigma + 0.15)</td>
<td>(-23.6\Delta \sigma + 3.5)</td>
<td>(-2.8\Delta \sigma + 0.90)</td>
<td>(-7.0\Delta \sigma + 0.69)</td>
</tr>
<tr>
<td>(R^2)</td>
<td>0.83</td>
<td>0.74</td>
<td>0.84</td>
<td>0.89</td>
<td>0.81</td>
<td>0.76</td>
<td>0.92</td>
</tr>
</tbody>
</table>

\(a\) All of the enthalpies are calculated at the B3LYP/6-31+G**//B3LYP/6-31G* level of theory.  
\(b\) Each function was obtained from a graph of \(\Delta H_0^{\text{meta}}\) vs \(\Delta \sigma\).

**Table 2.3.** Linear relationships between \(\Delta H_0^{\text{meta}}\) and \(\Delta \sigma (\Delta \sigma = \sigma_m - \sigma_p)\) \(^{40}\) for the substances shown in Scheme 2.3. \(a\)
From Table 2.3, for substituted nitrobenzene and nitrosobenzene, the slopes (3.7 and 3.6, respectively) are positive, suggesting that the magnitude of the substituent difference, $\Delta \sigma = \sigma_m - \sigma_p$, is inversely correlated with the stability of the meta-isomer relative to the para-isomer. This relationship can be explained by the electron-withdrawing nature of the nitro group and the nitroso group. Substituents that more efficiently withdraw electrons from the reaction site destabilize the reduction intermediates to a greater extent. For electron-rich compounds, such as the nitrobenzene radical anion, nitrosobenzene radical anion, phenylhydroxyamine, and aniline, electron-withdrawing substituents stabilize these types of compounds. The corresponding slopes of the plot of $\Delta H_0^{\text{meta}}$ versus $\Delta \sigma$ are negative, suggesting that the larger the difference between $\sigma_m$ and $\sigma_p$, the more stable the meta-isomer is in comparison to the para-isomer. The larger slope implies that the difference of $\sigma$ affects the relative stability of the two regioisomers to a greater extent. Consequently, small differences in the $\sigma$ value of the substituent can give rise to a significant change in the stability. The nitrobenzene radical anion and the nitrosobenzene radical anion exemplify this relationship (the slopes are $-22.7$ and $-23.6$, respectively). For the two radical intermediates shown in Table 2.3, the slopes for this relationship have small negative values. Thus, these species can be regarded as slightly electron-rich compounds. When there is no difference in the substituent constants, i.e., $\Delta \sigma = \sigma_m - \sigma_p = 0$, all of the intercepts at $\Delta H_0^{\text{meta}}$ are positive, thus the favored isomer is the para-isomer. For example, for the substituted nitro- and nitroso-benzene radical anions, the intercepts are +3.8 and +3.5 kcal/mol, respectively. The linear relationship between the theoretical calculation $\Delta H_0^{\text{meta}}$ and experimental data (the difference of $\sigma_m - \sigma_p$) may be extended to predict the stability of any meta-substituted benzene relative to
the corresponding para-substituted isomers if the substituent constants are known, or may be used to predict the substituent constant of any substituent by the calculation.

2.3.2 *Hammett correlations of each reduction step*

We have discussed how substituents at different positions can affect the stabilities of all of the substances generated in the reduction process of nitrobenzene. Now we will turn our attention to the substituent effects on each reaction shown in Scheme 2.3. There are seven steps for a nitro group to be reduced to an amino group. The substituent effects were determined through linear Hammett correlations: plotting the value of $\Delta(\Delta H_0)$, which is the difference between the $\Delta H_0$ of the reduction when the substituent $R = H$ and $\Delta H_0$ when $R \neq H$, versus $\sigma$ of the corresponding substituent; the slope of the obtained straight line is the reaction constant $\rho$. All of the $\rho$ values and the corresponding correlation coefficients for each reaction step, and the overall reduction, are listed in Table 2.4. The magnitude of $\rho$ reflects the sensitivity of the reduction to the substituent’s electronic effects: large $\rho$ indicate that the reaction is highly sensitive to substituent effects. The positive sign of the $\rho$ indicates that the corresponding reaction equilibrium increases with electron-withdrawing substituents. Conversely, a negative $\rho$ indicates the reaction equilibrium is favored by electron-donating substituents. From Table 2.4, all of the $R^2$ values are greater than 0.80, and most of them are greater than 0.90. Therefore, a good linear Hammett correlation for each reaction was obtained. As shown in Scheme 2.3, in step 1 and step 4, the substituted nitro- or nitroso-benzene accepts an electron from $H_2$ to form a radical anion. Consequently, substituents with strong electron-withdrawing
capabilities, i.e., with a large substituent constant $\sigma$, favor the reaction significantly. This can be seen from the reaction constant $\rho$ in the gas phase as both steps are very positive.

<table>
<thead>
<tr>
<th></th>
<th>Gas phase</th>
<th>Benzene$^a$</th>
<th>Water$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\text{Meta}$</td>
<td>$\text{Para}$</td>
<td>$\text{Meta}$</td>
</tr>
<tr>
<td>Step 1</td>
<td>25.0 (0.94)</td>
<td>29.8 (0.95)</td>
<td>17.7 (0.95)</td>
</tr>
<tr>
<td>Step 2</td>
<td>−22.2 (0.93)</td>
<td>−24.8 (0.94)</td>
<td>−14.4 (0.94)</td>
</tr>
<tr>
<td>Step 3</td>
<td>−2.1 (0.82)</td>
<td>−4.9 (0.92)</td>
<td>−2.4 (0.87)</td>
</tr>
<tr>
<td>Step 4</td>
<td>26.1 (0.96)</td>
<td>30.0 (0.97)</td>
<td>18.9 (0.97)</td>
</tr>
<tr>
<td>Step 5</td>
<td>−23.0 (0.96)</td>
<td>−25.3 (0.96)</td>
<td>−15.4 (0.97)</td>
</tr>
<tr>
<td>Step 6</td>
<td>2.3 (0.89)</td>
<td>3.2 (0.87)</td>
<td>2.7 (0.94)</td>
</tr>
<tr>
<td>Step 7</td>
<td>0.8 (0.92)</td>
<td>1.7 (0.94)</td>
<td>1.0 (0.91)</td>
</tr>
<tr>
<td>overall</td>
<td>6.9 (0.97)</td>
<td>9.7 (0.96)</td>
<td>8.0 (0.97)</td>
</tr>
</tbody>
</table>

$^a$ At the PCM(solvent)-B3LYP/6-31+G**//B3LYP(gas)/6-31G* level of theory.

**Table 2.4.** The reaction constant $\rho$ and the corresponding correlation coefficient ($R^2$, in parentheses) for the enthalpy ($\Delta H_0$) of each step shown in Scheme 2.3, as calculated at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level of theory.

For steps 2 and 5, $\rho$ values are very negative, indicating electron-donating substituents greatly favor the reactions. In these two steps, substituted nitro- or nitroso-benzene radical anion absorbs a proton and becomes a neutral radical. However, since there are no changes in charge in steps 3 and 6, the electron-withdrawing or -donating power of the
substituents do not affect the reaction energetics as much as in other steps mentioned above. For step 7, the small positive number $\rho$ value indicates that electron-withdrawing substituents favor this reaction, but not to a great extent. The overall reduction (Table 2.4, bold) of a nitro group to an amino group is favored by electron-withdrawing substituents as seen by the large, positive $\rho$ value for the overall reaction.

Substituent effects for para-substituted isomers play a more significant role during reduction than for the meta-substituted isomers. This is evident since the magnitudes of the reaction constants $\rho$ for all of the para-substituted reaction steps are always larger than that for the corresponding meta-substituted isomers. This is not particularly surprising, since substituents at para positions can exert both resonance and inductive effect while substituents at the meta-position affect reaction thermodynamics predominantly by induction.

We also investigated solvent effects on each reaction. All of the $\rho$ values and the corresponding correlation coefficients when the reaction is solvated by benzene and water are also listed in Table 2.4. When the dielectric constant increases from the gas phase to benzene to water, for the reaction steps with significant changes in molecular charge, such as steps 1, 2, 4 and 5, the magnitude of reaction constant $\rho$ is decreased [$\rho_{(gas)} > \rho_{(benzene)} > \rho_{(water)}$]. This can be rationalized by noting that the solvent with a larger dielectric constant can more readily stabilize the charged compounds. Consequently, the stabilizing contribution of substituents becomes less important. On the other hand, for the reduction steps without significant changes in molecular charge, the magnitude of $\rho$ is increased when the dielectric constant of the solvent increases, and this trend is more significant for the reactions of para-substituted substances than for the
meta-substituted compounds. For the overall reaction, the solvent with the larger dielectric constant significantly increases substituent effects on the reduction of both meta- and para-substituted nitrobenzene, and to a greater extent for the para-substituted nitrobenzene.

2.3.3 Comparison of the reduction of NPAHs and nitrated azaheterocycles with the reduction of nitrobenzene

Substituents on nitrobenzene have significant impact on the stability of all of the substances and on the reduction steps shown in Scheme 2.3. Environmental pollutants,\textsuperscript{41,42} such as nitrated polycyclic aromatic hydrocarbons (NPAHs) and nitrated aromatic azaheterocycles, can also exert their biological activity by undergoing nitro reduction.\textsuperscript{22} In order to comprehensively understand the reductive reaction, we carefully examined the reductions of NPAHs and the reduction of nitrated aromatic azaheterocycles, and compared the results with the reduction of nitrobenzene. The investigated NPAHs and nitrated azaheterocycles are shown in Figure 2.4. The relative reaction enthalpies at 0 K $\Delta(\Delta H_0)$, which equals the reaction enthalpy $\Delta H_0$ for the NPAHs or nitroquinoline or nitropyridine minus the reaction enthalpy $\Delta H_0$ for nitrobenzene, are listed in Table 2.5. When the $\Delta(\Delta H_0)$ value is negative, the reaction is more enthalpically favorable than nitrobenzene; conversely, when the $\Delta(\Delta H_0)$ value is positive, the reaction is less favored than for nitrobenzene.
Figure 2.4. Atomic numbering for nitronaphthalene, nitroanthracene, nitropyrene, nitrobiphenyl, nitroquinoline and nitropyridine.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Position</th>
<th>Step in the nitro group reduction$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>nitronaphthalene</td>
<td>1-nitro</td>
<td>-5.8 4.2 -1.4 -5.7 10.8 -2.4 -2.8 -3.2</td>
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<tr>
<td></td>
<td>2-nitro</td>
<td>-4.5 4.3 -0.7 -4.3 4.7 0.5 0.2 0.2</td>
</tr>
<tr>
<td>nitroanthracene</td>
<td>1-nitro</td>
<td>-11.5 8.9 -0.7 -10.1 10.0 3.0 -2.6 -3.1</td>
</tr>
<tr>
<td></td>
<td>2-nitro</td>
<td>-10.5 9.8 -0.7 -9.3 9.0 1.6 0.3 0.1</td>
</tr>
<tr>
<td></td>
<td>9-nitro</td>
<td>-9.3 10.4 -5.4 -11.2 7.9 5.0 -2.2 -4.8</td>
</tr>
<tr>
<td>nitropyrene</td>
<td>1-nitro</td>
<td>-11.9 10.2 -2.8 -10.7 9.0 3.9 -0.5 -2.8</td>
</tr>
<tr>
<td></td>
<td>2-nitro</td>
<td>5.3 -4.8 -0.6 -6.7 7.3 -0.3 -0.1 0.1</td>
</tr>
<tr>
<td></td>
<td>4-nitro</td>
<td>-10.0 8.2 -1.3 -10.0 14.8 -5.4 0.1 -3.7</td>
</tr>
<tr>
<td>nitrobenzene</td>
<td>2-nitro</td>
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</tr>
<tr>
<td></td>
<td>3-nitro</td>
<td>-2.5 2.5 -0.1 -3.1 3.2 -0.3 -0.01 -0.2</td>
</tr>
<tr>
<td></td>
<td>4-nitro</td>
<td>-5.4 5.5 -0.3 -5.4 5.2 0.7 -0.1 0.3</td>
</tr>
<tr>
<td>nitropyridine</td>
<td>2-nitro</td>
<td>-3.2 0.5 2.6 -6.6 0.1 -2.3 -0.5 -9.4</td>
</tr>
<tr>
<td></td>
<td>3-nitro</td>
<td>-6.6 5.5 0.4 -7.2 5.9 -0.4 -0.2 -2.7</td>
</tr>
<tr>
<td></td>
<td>4-nitro</td>
<td>-11.2 8.5 3.0 -12.3 9.8 -3.0 -1.0 -6.2</td>
</tr>
<tr>
<td>nitroquinalide</td>
<td>2-nitro</td>
<td>-8.5 1.4 6.6 -10.9 9.3 -6.9 -0.9 -9.8</td>
</tr>
<tr>
<td></td>
<td>3-nitro</td>
<td>-10.7 9.8 0.2 -11.8 10.2 0.4 -0.03 -2.0</td>
</tr>
<tr>
<td></td>
<td>4-nitro</td>
<td>-16.0 11.9 1.9 -17.1 20.0 -5.7 -3.7 -8.7</td>
</tr>
<tr>
<td>nitrobenzene</td>
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</tr>
<tr>
<td></td>
<td>6-nitro</td>
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</tr>
<tr>
<td></td>
<td>7-nitro</td>
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</tr>
<tr>
<td></td>
<td>8-nitro</td>
<td>-3.8 -6.5 7.9 -6.54 3.5 -5.4 -0.6 -11.4</td>
</tr>
</tbody>
</table>

$^a$ See Scheme 2.3 for the steps of the reduction process.

**Table 2.5.** The reaction enthalpies of nitrated arenes and nitrated azaheterocycles at 0 K [$\Delta(\Delta H_0)$, kcal/mol] relative to the reaction enthalpies of nitrobenzene for each step (Scheme 2.3), as calculated at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level of theory.
As shown in Table 2.5, for the reduction of 1-nitronaphthalene, each step, except for steps 2 and 5, has a more favorable driving force than nitrobenzene. Therefore, the fused benzene ring behaves as an electron-withdrawing group. For 2-nitronaphthalene, steps 1, 3, and 4 are more downhill than for nitrobenzene; for steps 2 and 5, the reduction is less favored; for steps 6 and 7 along with the overall reduction from nitro to amine, the energetics are essentially indistinguishable from nitrobenzene.

For the reduction of 1-nitroanthracene, 9-nitroanthracene, 1-nitropyrene and 4-nitropyrene, the fused naphthalene ring or fused phenanthrene ring behaves as an electron-withdrawing group and increases the enthalpic favorability of the reductions. For the reduction of 2-nitroanthracene and 2-nitropyrene, the overall reaction energetics are almost indistinguishable from that of nitrobenzene. For the reduction of 2- and 3-nitrobiphenyl, the \( \Delta(\Delta H_0) \) for steps 1 and 4 along with the overall reaction are negative, and the \( \Delta(\Delta H_0) \) for steps 2 and 5 are positive. When the nitro group is at the 4-position, the overall reduction is almost the same as for nitrobenzene.

For the reduction of the nitrated azaheterocycles, nitropyridine and nitroquinoline, the nitrogen atom in the rings acts as a strong electron-withdrawing group for each step and the overall reaction, only with one exception, that being 8-nitroquinoline. For 8-nitroquinoline, the overall reduction is much more favored than nitrobenzene, but the \( \Delta(\Delta H_0) \) for step 2 is unexpectedly negative.

From the analyses presented above, in general, NPAHs and nitrated aromatic azaheterocycles appear to have more favorable reduction energetics than nitrobenzene. This presents a simple explanation of why they are more toxic, more mutagenic and more carcinogenic than nitrobenzene.\(^{43}\)
2.4 Conclusions

In this study, detailed information regarding quantitative energetic changes during the reductive conversion of the substituted nitrobenzenes, various nitrated polycyclic aromatic hydrocarbons (NPAHs), and a few nitrated aromatic azaheterocycles to the corresponding arylamines were determined.

Substituent effects on the stability of the ortho-isomer are mainly attributed to steric effects, electrostatic effects and hydrogen bonding. Most of the ortho-substituted nitroarenes and their derivatives are higher in energy than the para-substituted isomers and meta-substituted isomers, which we attribute to a combination of steric and electronic effects. For meta-substituted nitrobenzenes, nitrosobenzenes, hydroxylaminobenzenes and anilines, a linear relationship between $\Delta H_0^{\text{meta}}$ [$\Delta H_0 = H_0(\text{meta}) - H_0(\text{para})$] and the charge differences on the carbon bonded to the reaction site was found. Additionally, a linear relationship between $\Delta H_0^{\text{meta}}$ and $\Delta\sigma$ ($\Delta\sigma = \sigma_m - \sigma_p$) were found for all types of substances generated in the reduction process shown in Scheme 2.3. These two relationships can quantitatively explain the relative stability of the meta-isomers.

We also studied the substituent effects on each reaction shown in Scheme 2.3, and a linear Hammett correlation for each reaction was obtained. Solvent effects on the Hammett correlations were also studied, and in a reductive reaction with significant charge changes, the increase of dielectric constants of the solvent will decrease the substituent effects.

We also examined the reduction of the larger ring systems, such as nitronaphthalene, nitroanthracene, nitropyrene and nitrobiphenyl, as well as the reduction
of nitrated aromatic azaheterocycles, such as nitropyridine and nitroquinoline, and we compared the results with the reduction of nitrobenzene itself. The effect of a large arene is dependent on the position of the nitro group, but generally, the larger NPAHs are more feasible to be reduced than nitrobenzene. For the reduction of nitrated azaheterocycles, nitropyridine and nitroquinoline, the nitrogen atom in the ring acts like an electron-withdrawing group and makes the reduction more favored than the reduction of nitrobenzene. Thus, NPAHs and nitrated aromatic azaheterocycles should be more toxic, more mutagenic and more carcinogenic than nitrobenzene.

2.5 References


(b) Onchoke, K. K.; Hadad, C. M.; Dutta, P. K. *Polycyclic Aromatic Compounds*, **2004**, 24, 37-64,  


3.1 Introduction

The carcinogenicity and mutagenicity of atmospheric organic particulate matter, as manifested in experimental animals, has generally been attributed to the presence of polycyclic aromatic hydrocarbons (PAH) as well as their azaheterocyclic analogs in polluted air.\textsuperscript{1-6} PAH compounds exert their biological activity through metabolic activation, which produces reactive intermediates to attack biological macromolecules, such as DNA.\textsuperscript{7,8} The biological oxidation of PAHs is first catalyzed by the cytochrome P-450 monooxygenases to produce epoxides,\textsuperscript{9-11} as shown in Figure 3.1,\textsuperscript{12} followed by epoxide hydrase enzyme-mediated hydrolysis to the trans diols, and a second epoxidation at the adjacent double bond. This metabolic process yields a diol-epoxide which then interacts with nucleophilic DNA, giving rise to the alkylation of DNA thus resulting in carcinogenicity and mutagenicity.\textsuperscript{12-14} In 1968, Jerina \textit{et al.} isolated naphthalene-1,2-oxide as a metabolite of naphthalene and provided some evidence for this proposal.\textsuperscript{15} Depending on their location within a given PAH, the diol-epoxide derivatives exhibit different biological activities; generally, the bay-region derivatives exhibit higher mutagenic and carcinogenic activity.\textsuperscript{16} This finding illustrates the importance of the
regioselectivity of the first step (i.e., epoxidation), since it largely determines which diol-epoxide will be generated. The instability of these first-step epoxides in biological systems prove to be a challenge in their preparation and characterization, and thus for studying PAHs, computational methods constitute important tools.

Figure 3.1. Metabolic activation pathways of PAHs leading to the formation of a diol-epoxide, a precursor electrophile for the formation of DNA adducts.\textsuperscript{12} P-450 refers to oxidation by cytochrome P450 monooxygenases, and EH refers to the conversion by epoxide hydrase.

Several theoretical studies related to PAHs have been reported.\textsuperscript{16} Besides many semiempirical calculations, ab initio and some density functional theory calculations have been used.\textsuperscript{12,17-22a,22b} Borosky applied quantum mechanical methods to a study of the main factors determining the ring-opening reactivity of arene-epoxides (the second steps in Figure 3.1) and the ring-opening of diol-epoxides and thus explored the relationship between the structures of arene-epoxides or diol-epoxides and the carcinogenic activity of PAHs.\textsuperscript{12} Alberto utilized the hybrid density functional method B3LYP with the 6-31+G* basis set and reproduced the gas-phase experimental adiabatic electron affinities (AEAs) for eleven PAHs.\textsuperscript{22c} Because comprehensive and systematic theoretical studies on both the first step of oxidation in Figure 3.1, and the regioselectivities for oxidation of PAHs...
are lacking, herein, we report our computational results on these epoxidation reactions of PAHs, as well as the regioselectivities of the epoxidation and solvation effects on these reactions. Where available, these computational results are compared to available experimental data.

3.2 Computational Methods

Hydroperoxy radical is a common oxidant in biological systems. Therefore, in this computational study, it is the oxidant used to transform PAHs to the corresponding epoxides, as depicted below (Figure 3.2). Since this study is a thermodynamic investigation, the qualitative and relative trends for the oxidation of different PAHs is independent of the oxidant used in Figure 3.2; however, this scheme seemed reasonable, is computationally tractable, and is reminiscent of the oxidative components involved in cytochrome P-450 enzymes.

\[
\text{PAH} + \text{HO}_2^\cdot \rightarrow \text{PAH-epoxide} + \text{HO}^\cdot
\]

**Figure 3.2.** Chemical equation for the transformation of PAHs to the corresponding epoxides, using the common oxidant, hydroperoxy radical.

Hybrid density functional theory (DFT) was employed to obtain optimized geometries and vibrational frequencies for all stationary points at the B3LYP/6-31G*
level of theory.\textsuperscript{24} Single-point energies were obtained at the B3LYP/6-31+G** level\textsuperscript{25} using the optimized B3LYP/6-31G* geometries. In order to consider the different dielectric constant of an enzyme’s active site as well as bulk water, the effect of solvation was investigated with the polarizable continuum model (PCM) for benzene and water using single-point energy calculations at the B3LYP/6-31+G** level and with the gas-phase optimized geometries.\textsuperscript{26} All calculations were performed with Gaussian 03.\textsuperscript{27}

All reactants and products were confirmed to be energetic minima via vibrational frequency analyses at the B3LYP/6-31G* level of theory. Scaling factors of 0.9806\textsuperscript{28} were used for the zero-point vibrational energy (ZPE) correction for the B3LYP/6-31G* geometries. Reaction enthalpies and free energies at 298 K ($\Delta H_{298}$ and $\Delta G_{298}$, respectively) were obtained from the calculated thermal and entropic correction using the unscaled vibrational frequencies. Reaction enthalpies at 0 K ($\Delta H_0$) are calculated from single-point energies and scaled zero-point energies. In this paper, since $\Delta H_{298}$, $\Delta G_{298}$ and $\Delta H_0$ values follow the same trends, we will confine our discussion to the $\Delta H_0$ values for the reactions of interest, unless otherwise noted. All values are included in the Supporting Information.

### 3.3 Results and Discussion

#### 3.3.1 Epoxidation of benzene

Before turning our attention to the larger systems that govern much of PAH chemistry, we will first discuss the results obtained for benzene. Benzene is the simplest aromatic compound and cannot demonstrate epoxidation regioselectivity. The oxidation
enthalpies at 0 K and 298 K, and the free energies at 298 K, are listed in Table 3.1 for benzene in the gas phase and in water.

<table>
<thead>
<tr>
<th></th>
<th>Gas Phase</th>
<th>Benzene</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta H_0$</td>
<td>12.61</td>
<td>12.24</td>
<td>11.68</td>
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<tr>
<td>$\Delta H_{298}$</td>
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<td>14.35</td>
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<tr>
<td>$\Delta G_{298}$</td>
<td>14.07</td>
<td>13.70</td>
<td>13.14</td>
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</table>

**Table 3.1.** Oxidation energies ($\Delta H_0$, $\Delta H_{298}$ and $\Delta G_{298}$, kcal/mol) for the reactions of benzene using hydroperoxy radical as an oxidant as shown in Figure 3.2, calculated at the B3LYP/6-31+G(d,p)// B3LYP/6-31G(d) level in both the gas phase and with the PCM model for solvation.

From Table 3.1, $\Delta H_0$, $\Delta H_{298}$ and $\Delta G_{298}$ values for the epoxidation reaction of benzene have the same trends from the gas phase to benzene to water; i.e., as the dielectric constant of the solvent increases, the magnitudes of $\Delta H_0$, $\Delta H_{298}$ and $\Delta G_{298}$ decrease, demonstrating that benzene will be more favorably oxidized in a more polar environment.

### 3.3.2 Epoxidation of larger polycyclic aromatic hydrocarbons

The epoxidation of larger polycyclic aromatic hydrocarbons, such as naphthalene, anthracene, phenanthrene and pyrene (shown in Figure 3.3), was also examined.
Figure 3.3. Atomic numbering for naphthalene, anthracene, phenanthrene and pyrene

All of the oxidation enthalpies at 0 K ($\Delta H_0$) are listed in Table 3.2. For naphthalene and anthracene, while oxidation can occur at the 1,2- and 2,3-positions, oxidation at the 1,2-position is the most thermodynamically favored in the gas phase. This regioselectivity can be mainly attributed to the aromaticity preserved in the untouched benzene and naphthalene ring, respectively. When we tried to optimize the geometry of anthracene-2,3-epoxide, However, our geometry optimizations returned a seven-membered ring, i.e., an oxepine, as shown in Figure 3.4, rather than the expected 2,3-epoxide from anthracene. One likely reason is that the 2,3-epoxide would not exhibit the aromaticity of the naphthalene system resulting from the two unoxidized rings, while the seven-membered oxepine retains some aromaticity.
<table>
<thead>
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<th>Compound</th>
<th>Epoxidation position</th>
<th>Gas phase</th>
<th>Benzene</th>
<th>Water</th>
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<tbody>
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<td>1,2-position</td>
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<td>12.24</td>
<td>11.68</td>
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<td>15.64</td>
<td>10.84</td>
</tr>
<tr>
<td></td>
<td>3,4-position</td>
<td>5.39</td>
<td>2.53</td>
<td>−2.34</td>
</tr>
<tr>
<td></td>
<td>9,10-position</td>
<td>−3.85</td>
<td>−6.75</td>
<td>−11.73</td>
</tr>
<tr>
<td>Pyrene</td>
<td>1,2-position</td>
<td>10.56</td>
<td>10.24</td>
<td>9.74</td>
</tr>
<tr>
<td></td>
<td>4,5-position</td>
<td>−4.59</td>
<td>−4.93</td>
<td>−5.48</td>
</tr>
</tbody>
</table>

\(^a\) Geometry optimizations of this epoxide yielded the corresponding seven-membered ring oxepine instead of the epoxide.

**Table 3.2.** Oxidation enthalpies (\(\Delta H_0\), kcal/mol) of PAHs (benzene, naphthalene, anthracene, phenanthrene and pyrene) using hydroperoxy radical as an oxidant as shown in 3.2, calculated at the B3LYP/6-31+G(d,p)// B3LYP/6-31G(d) level in both the gas phase and with the PCM model for solvation.

**Figure 3.4.** Oxepine obtained after attempts to minimize the geometry of the 2,3-epoxide derived from anthracene.

Phenanthrene is an angular polycyclic species, while naphthalene and anthracene are linear. This fact leads to some heretofore unseen results. For phenanthrene, the
potential epoxide products can be located at multiple positions, specifically either 1,2; 2,3; 3,4; or 9,10. Of these, the 9,10-epoxide derived from phenanthrene is the most thermodynamically favored. This regioselectivity is also attributed to the relative aromaticity of the potential products. When oxidation occurs at the 2,3-position of phenanthrene, only one benzene ring is preserved; when oxidation occurs at the 1,2-position or 3,4-position, the naphthalene moiety is preserved; when oxidation occurs at the 9,10-position, two benzene rings are preserved. This implies that the aromaticity of two benzene rings is stronger than the aromaticity of one naphthalene and the aromaticity of one naphthalene is stronger than the aromaticity of one benzene. These implications are consistent with estimates of the resonance stabilization energies of these aromatic systems.\(^\text{29}\) For pyrene, the other angular PAH considered here, oxidation can occur at the 1,2-position or the 4,5-position, but the 4,5-position is much more readily oxidized. Once again, the regioselectivities can be mainly attributed to the aromaticity of the remaining phenanthrene ring when the 4,5-position is oxidized.

In the condensed phase, the qualitative trends of the oxidation’s $\Delta H_0$ values for all of the PAHs of interest are preserved and thus the regioselectivities are not affected by solvation. For these PAHs, as the dielectric constant of the solvent increases, $\Delta H_0$ decreases: these PAHs are more readily oxidized in the solvents with larger dielectric constants when hydroperoxy radical is used as an oxidant as shown in Figure 3.2. The most significant solvent effects can be seen for the epoxidation of phenanthrene.
3.3.3. Comparison of the calculation results with experimental data

Since Jerina et al. isolated naphthalene-1,2-oxide as a metabolite of naphthalene in 1968,\textsuperscript{15} oxidations of PAHs have been of substantial research interest. Boyd et al. have chemically synthesized naphthalene-1,2-oxide and anthracene-1,2-oxide;\textsuperscript{30} Hamilton et al. have produced phenanthrene-9,10-epoxide and pyrene-4,5-epoxide by using NaClO\textsubscript{2} as the oxidant;\textsuperscript{31} Van Bladeren et al. have bio-synthesized naphthalene-1,2-oxide and anthracene-1,2-oxide.\textsuperscript{32} Although PAHs can be oxidized at various positions, all of the methods above only produced one predominant epoxide. The regioselectivities seen in this experimental work parallel the results we obtained computationally, thus verifying our computational approach. Moreover, it is evident that these chemical and biological transformations are dominated by thermodynamic effects of the epoxide products.

3.4 Conclusions

Our DFT (B3LYP/6-31+G**//B3LYP/6-31G* and PCM/B3LYP/6-31+G**//B3LYP/6-31G*) studies of the epoxidations of PAHs reveal that these processes are regioselective oxidations that occur in such a manner as to maximize the remaining aromaticity in these systems, and the oxidation process tends to favor the preservation of two benzene rings over one naphthalene ring, and one naphthalene ring over one benzene ring. In the condensed phase, the oxidations in the system as shown in Figure 3.2, especially for the oxidation of phenanthrene, become more favorable with increasing dielectric constant of the medium. Qualitative $\Delta H_0$ trends for all PAHs are preserved regardless of the solvent used; the regioselectivities are not affected by
solvents. The regioselectivities obtained from our computational method were compared with extant experimental data and were seen to be consistent with each other. Thus, epoxidation of PAHs appears to proceed under thermodynamic control, and formation of the most stable epoxide is favored.

3.5 References


CHAPTER 4

COMPUTATIONAL EXPLORATIONS OF THE REGIOSELECTIVE EPOXIDATION OF NITRATED POLYCYCLIC AROMATIC HYDROCARBONS

4.1 Introduction

Nitratated polycyclic aromatic hydrocarbons (NPAHs)\textsuperscript{1-2} and polycyclic aromatic hydrocarbons (PAHs)\textsuperscript{3-4} are well-known environmental pollutants. While NPAHs and other PAHs usually result from incomplete combustion processes, such as the emissions from diesel combustion, they can also be formed by the reactions of parent PAHs with reactive nitrogen-containing species existing in the atmosphere.\textsuperscript{5-13} NPAHs are found both in urban and rural areas.\textsuperscript{14-19} Although the concentrations of NPAHs are somewhat lower than those of their parent PAHs,\textsuperscript{20} some NPAHs have been found to have higher toxicity than their parent PAHs.\textsuperscript{10,21} Consequently, this class of chemical carcinogens has attracted increasing attention in recent years.

Both PAHs and NPAHs generally exert their biological activity through metabolic activation, which produces reactive intermediates to attack biological molecules, especially DNA.\textsuperscript{22-23} The presence of the nitro groups makes the metabolism of NPAHs more complicated than that of their parent PAHs. In addition to ring oxidation, NPAHs may undergo reduction of the nitro group, or a combination of ring oxidation and nitro
Using benzo[a]pyrene (BaP) as an example, Scheme 4.1 shows sample metabolically activated pathways of NPAHs leading to the formation of DNA adducts and the subsequent induction of mutation in CHO cells. In the nitro-reduction pathway, the nitro group is reduced to a nitroso functionality, then to a hydroxylamine, and subsequently to a substituted nitrenium ion, which can react as a potent electrophile with DNA to form DNA adducts. In the oxidative pathway, three steps are needed to activate NPAHs to ultimately form carcinogens: (1) cytochrome P450 monooxygenase-mediated epoxidation, (2) epoxide hydrase enzyme-catalyzed ring-opening of the resultant epoxide to a trans diol, and (3) a second epoxidation of the adjacent double bond. The generated diol-epoxide, a potent electrophile, can interact with DNA as an electrophile, leading to alkylated DNA.
Scheme 4.1. Metabolically activated pathways of 1-nitro-BaP leading to the formation of DNA adducts and the subsequent induction of mutation in CHO cells, as proposed by Zhan et al.\textsuperscript{24}

Depending on their location within a given PAH or NPAH, the diol-epoxide derivatives exhibit different biological activity; generally, the bay-region derivatives exhibit higher mutagenic and carcinogenic activity.\textsuperscript{25} This finding illustrates the importance of predicting the regioselectivity of the first-step epoxidation, since it largely determines what diol-epoxide will be subsequently generated. Computational methods constitute important tools for studying NPAHs and their epoxidation reactions, due to the
instability of these epoxides and the attendant challenges in their preparation and characterization.

Several theoretical studies related to PAHs have been reported. Besides many semiempirical calculations, ab initio and some density functional theory calculations have been used. These studies have greatly enriched our understanding of the relationship between biological activity of PAHs with their electronic and structural properties. For example, Tian et al. calculated the oxidation enthalpies at 0 K of PAHs at the B3LYP/6-31+G**//B3LYP/6-31G* level of theory and found various epoxidation regioselectivities, all of which were consistent with available biological experimental data. These authors also successfully explained the correlation between the regioselectivities of the epoxidation and the structure of PAHs. No work has similarly explored the oxidation of nitrated polyaromatic hydrocarbons, i.e., NPAHs, in such a systematic fashion. Recently, we studied the nitro-reduction pathway of NPAHs using density functional theory calculations (also at the B3LYP/6-31+G**//B3LYP/6-31G* level of theory).

Given our ongoing interest in NPAHs, we would like to extend this computational approach (B3LYP/6-31+G**//B3LYP/6-31G*) to the origin of the regioselectivity of the epoxidation (first step) in the metabolism of NPAHs. Herein, we report our computational results on the epoxidation regioselectivities and the effects of the nitro group and solvation on the regioselectivities and epoxidation preferences for NPAHs relative to unsubstituted PAHs.
4.2 Computational Methods

Hydroperoxyl radical is a common oxidant in biological systems.\textsuperscript{32} Therefore, in this computational study, it is the oxidant used to transform NPAHs to the corresponding epoxides, as depicted below (Figure 4.1). Since this study is a thermodynamic investigation, the qualitative and relative trends for the oxidation of different NPAHs is independent of the oxidant used in Figure 4.2; however, this scheme seemed reasonable, is computationally tractable, and is reminiscent of the oxidative components involved in cytochrome P-450 enzymes.

\begin{equation}
\text{O}_2\text{N} + \text{HO}_2^+ \rightarrow \text{O}_2\text{N} + \text{HO}^-
\end{equation}

\textbf{Figure 4.1.} Chemical equation for the transformation of NPAHs to corresponding epoxides, using the common oxidant, hydroperoxyl radical.

Hybrid density functional theory (DFT) was employed to obtain optimized geometries and vibrational frequencies for all stationary points at the B3LYP/6-31G* level of theory.\textsuperscript{33} Single-point energies were obtained at the B3LYP/6-31+G** level\textsuperscript{34} based on the optimized B3LYP/6-31G* geometries. The effect of solvation was investigated with the polarizable continuum model (PCM) for water and benzene using single-point energy calculations at the B3LYP/6-31+G** level and using the gas-phase optimized geometries.\textsuperscript{35} All calculations were performed with Gaussian 03.\textsuperscript{36}
All reactants and products were confirmed to be energetic minima via vibrational frequency analyses at the B3LYP/6-31G* level of theory. Scaling factors of 0.9806 were used for the zero-point vibrational energy (ZPE) correction for the B3LYP/6-31G* geometries. Reaction enthalpies and free energies at 298 K ($\Delta H^{\text{298}}$ and $\Delta G^{\text{298}}$ respectively) were obtained from the calculated thermal and entropic corrections using the unscaled vibrational frequencies. Reaction enthalpies at 0 K ($\Delta H^{0}$) are calculated from the single-point energies and scaled zero-point energies. In this paper, because $\Delta H^{\text{298}}$ and $\Delta G^{\text{298}}$ values have the same trends as $\Delta H^{0}$, for convenience, only $\Delta H^{0}$ values are discussed in the subsequent text, and $\Delta H^{\text{298}}$ and $\Delta G^{\text{298}}$ values are provided in the supporting information.

In many cases, the nitro group of the relevant NPAH is not coplanar with the ring system, resulting in two diastereomeric epoxide products, and these isomers were considered. However, as the calculated energetic difference between these diastereomers is small, the computational data for the most stable diastereomer will be discussed.

### 4.3 Results and Discussion

#### 4.3.1 Nitrobenzene

We will first discuss the results obtained for nitrobenzene, before turning our attention to the larger systems that govern much of the NPAH chemistry.

Nitrobenzene can be oxidized at three chemically distinct sites, yielding three potential oxidation products as shown in Figure 4.2: 1,2-nitrobenzene epoxide, 2,3-nitrobenzene epoxide, and 3,4-nitrobenzene epoxide.
Figure 4.2. The optimized geometries of the 1,2- (left), 2,3- (middle) and 3,4- (right) nitrobenzene epoxides at the B3LYP/6-31G* level of theory. The C2–C1–N–O dihedral angle (τ, in degrees) is shown.

The oxidation enthalpies (ΔH₀) of nitrobenzene in the gas phase, benzene and water are listed in Table 4.1; the oxidation enthalpies of benzene, the parent PAH, are listed in parentheses for comparison.

<table>
<thead>
<tr>
<th>Epoxidation position</th>
<th>Gas phase</th>
<th>Benzene⁹</th>
<th>Water⁹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-position</td>
<td>14.15 (12.61)</td>
<td>14.43 (12.24)</td>
<td>14.61 (11.68)</td>
</tr>
<tr>
<td>2,3-position</td>
<td>12.49 (12.61)</td>
<td>12.19 (12.24)</td>
<td>11.62 (11.68)</td>
</tr>
<tr>
<td>3,4-position</td>
<td>13.71 (12.61)</td>
<td>13.68 (12.24)</td>
<td>13.50 (11.68)</td>
</tr>
</tbody>
</table>

⁹ At the PCM(solvent)-B3LYP/6-31+G**//B3LYP(gas)/6-31G* level of theory.

Table 4.1. Oxidation enthalpies (ΔH₀, kcal/mol, B3LYP/6-31+G**//B3LYP/6-31G*) for the reactions of nitrobenzene with hydroperoxyl radical (Figure 4.1) and comparison with the oxidation of benzene (in parentheses).
Epoxidation of nitrobenzene at the 2,3-position is the most thermodynamically favored. This regioselectivity can be due to the favorable resonance interactions between the nitro group and the ring. In 1-nitrobenzene-1,2-epoxide, because the newly generated epoxide ring is rigid, the nitro group is out of the cyclohexadiene plane (see Figure 4.2: the C2–C1–N–O dihedral angle is −13.2°), and the nitro group can not conjugate with any of double bonds existing in the six-membered carbon ring. When the oxidation occurs at the 2,3-position, the nitro group is almost coplanar with the other two double bonds (the C2–C1–N–O dihedral angle is 4.7°), and the nitro group can conjugate with both double bonds. For the 3,4-epoxide, although the nitro group is almost coplanar with the cyclohexadiene unit (the C2–C1–N–O dihedral angle is −2.8°), the nitro group can only conjugate with one double bond of the cyclohexadiene unit. Compared with benzene, the oxidation of nitrobenzene in the 2,3-position is slightly more exothermic, but all of the other oxidative pathways are less favored relative to benzene.

In the condensed phase, the regioselectivity remains the same (i.e., the 2,3-position of nitrobenzene is the most favored epoxide). As the dielectric constant of the solvent increases, i.e., from the gas phase to benzene to water, ΔH₀ increases and the oxidation is less favored at the 1,2-position. For the oxidations at the 2,3- and 3,4-positions, however, when the dielectric constant of the solvent increases, ΔH₀ decreases and nitrobenzene is more favorably oxidized, an effect also seen for benzene.
4.3.2 *Nitronaphthalene*

The locants on nitronaphthalene are labeled in Figure 4.3.

![Nitronaphthalene and its numbering.](image)

**Figure 4.3.** Nitronaphthalene and its numbering.

Two isomers of nitronaphthalene exist: 1-nitronaphthalene and 2-nitronaphthalene. In either isomer, oxidation can occur at the 1,2; 2,3; 3,4; 5,6; 6,7; or 7,8 locations. The relevant enthalpies of the reaction are summarized in Table 4.2; again, for comparison, the corresponding results for the parent hydrocarbon are included in parentheses.
### 1-nitronaphthalene

<table>
<thead>
<tr>
<th>Epoxidation position</th>
<th>Gas phase</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-position</td>
<td>2.83 (2.19)</td>
<td>2.97 (1.81)</td>
<td>2.94 (1.23)</td>
</tr>
<tr>
<td>2,3-position</td>
<td>20.17 (22.45)</td>
<td>19.58 (22.20)</td>
<td>18.55 (21.78)</td>
</tr>
<tr>
<td>3,4-position</td>
<td>4.41 (2.19)</td>
<td>4.37 (1.81)</td>
<td>4.21 (1.23)</td>
</tr>
<tr>
<td>5,6-position</td>
<td>3.59 (2.19)</td>
<td>3.48 (1.81)</td>
<td>3.29 (1.23)</td>
</tr>
<tr>
<td>6,7-position</td>
<td>22.35 (22.45)</td>
<td>22.05 (22.20)</td>
<td>21.45 (21.78)</td>
</tr>
<tr>
<td>7,8-position</td>
<td>3.45 (2.19)</td>
<td>3.46 (1.81)</td>
<td>3.43 (1.23)</td>
</tr>
</tbody>
</table>

### 2-nitronaphthalene

<table>
<thead>
<tr>
<th>Epoxidation position</th>
<th>Gas phase</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-position</td>
<td>4.25 (2.19)</td>
<td>4.59 (1.81)</td>
<td>4.89 (1.23)</td>
</tr>
<tr>
<td>2,3-position</td>
<td>24.37 (22.45)</td>
<td>24.76 (22.20)</td>
<td>25.15 (21.78)</td>
</tr>
<tr>
<td>3,4-position</td>
<td>2.07 (2.19)</td>
<td>1.72 (1.81)</td>
<td>1.16 (1.23)</td>
</tr>
<tr>
<td>5,6-position</td>
<td>3.15 (2.19)</td>
<td>2.99 (1.81)</td>
<td>2.66 (1.23)</td>
</tr>
<tr>
<td>6,7-position</td>
<td>22.52 (22.45)</td>
<td>22.28 (22.20)</td>
<td>21.81 (21.78)</td>
</tr>
<tr>
<td>7,8-position</td>
<td>2.75 (2.19)</td>
<td>2.49 (1.81)</td>
<td>2.00 (1.23)</td>
</tr>
</tbody>
</table>

<sup>a</sup> At the PCM(solvent)-B3LYP/6-31+G**//B3LYP(gas)/6-31G* level of theory.

**Table 4.2.** Oxidation enthalpies ($\Delta H_0$, kcal/mol, B3LYP/6-31+G**//B3LYP/6-31G*) for the reactions of nitronaphthalenes with hydroperoxyl radical (Figure 4.1) and comparison with the oxidation of naphthalene (in parentheses).
In 1-nitronaphthalene, oxidation at the 1,2-position is the most thermodynamically favored. Compared to naphthalene, 1-nitronaphthalene is less feasibly oxidized at the 1,2-, 3,4-, 5,6- and 7,8-positions regardless of environment, while the oxidation is more favored when oxidation occurs at the 2,3- and 6,7-positions. For 2-nitronaphthalene, the most favored position of epoxidation is the 3,4-position regardless of solvation, and epoxidation of the NPAH is more favored than that of the parent PAH. When oxidation occurs at the other positions, those are less favored than the parent compound. When either nitronaphthalene is oxidized at the 1,2-, 3,4-, 5,6-, or 7,8-positions, the aromaticity from the other ring is preserved; thus, oxidation at these positions is much more favored than at the 2,3- and 6,7-positions. In addition, the inductive effect of the nitro group may also play an important role in these regioselectivities. For both 1-nitronaphthalene and 2-nitronaphthalene, the oxidation preferably occurs on the same ring as the nitro group.

In the condensed phase, the solvation effect is complicated. The 1,2-position of 1-nitronaphthalene along with the 1,2- and 2,3-positions of 2-nitronaphthalene are less favorably oxidized when the dielectric constant of the solvent increases. The oxidation of the 7,8-position of 1-nitronaphthalene is not significantly affected by solvation. For the oxidation at the other positions of both 1-nitronaphthalene and 2-nitronaphthalene, epoxidation is more favored in the more polar solvent. Nevertheless, all of these effects are small (<1 kcal/mol), and the regioselectivities remain the same when the dielectric constant of the solvent changes.
4.3.3 Nitroanthracene

The locants on nitroanthracene are labeled in Figure 4.4.

![Nitroanthracene and its numbering.](image)

**Figure 4.4.** Nitroanthracene and its numbering.

Nitroanthracene exists in three isomeric forms: 1-nitroanthracene, 2-nitroanthracene and 9-nitroanthracene. Oxidation can theoretically occur at the 1,2-, 2,3-, 3,4-, 5,6-, 6,7-, or 7,8-position for each isomer. However, our geometry optimizations returned seven-membered ring products (oxepines, shown in Figure 4.5) rather than the expected 2,3-epoxides and 6,7-epoxides of the nitroanthracenes.

![Exemplary geometries of the resulting oxepines.](image)

**Figure 4.5.** Exemplary geometries of the resulting oxepines obtained after attempts to minimize the geometries of 2,3- and 6,7-epoxides of the corresponding nitroanthracenes.
One likely reason is that the 2,3- and 6,7-epoxides would not exhibit the aromaticity of the naphthalene system resulting from the two unoxidized rings, while the seven-membered oxepines retain this aromaticity. The oxidation enthalpies ($\Delta H_0$) of 1-nitroanthracene, 2-nitroanthracene and 9-nitroanthracene in the gas phase, benzene and water have been calculated (Table 4.3). The oxidation enthalpies ($\Delta H_0$) of the parent PAH, anthracene, are also listed for comparison.
### 1-nitroanthracene

<table>
<thead>
<tr>
<th>Epoxidation position</th>
<th>Gas phase</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-position</td>
<td>−0.71 (&lt;1.81)</td>
<td>−0.56 (&lt;2.20)</td>
<td>−0.49 (&lt;2.80)</td>
</tr>
<tr>
<td>2,3-position&lt;sup&gt;b&lt;/sup&gt;</td>
<td>———</td>
<td>———</td>
<td>———</td>
</tr>
<tr>
<td>3,4-position</td>
<td>0.61 (&lt;1.81)</td>
<td>0.64 (&lt;2.20)</td>
<td>0.62 (&lt;2.80)</td>
</tr>
<tr>
<td>5,6-position</td>
<td>−1.31 (&lt;1.81)</td>
<td>−1.55 (&lt;2.20)</td>
<td>−1.96 (&lt;2.80)</td>
</tr>
<tr>
<td>6,7-position&lt;sup&gt;b&lt;/sup&gt;</td>
<td>———</td>
<td>———</td>
<td>———</td>
</tr>
<tr>
<td>7,8-position</td>
<td>−1.11 (&lt;1.81)</td>
<td>−1.33 (&lt;2.20)</td>
<td>−1.76 (&lt;2.80)</td>
</tr>
</tbody>
</table>

### 2-nitroanthracene

<table>
<thead>
<tr>
<th>Epoxidation position</th>
<th>Gas phase</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-position</td>
<td>0.60 (&lt;1.81)</td>
<td>0.97 (&lt;2.20)</td>
<td>1.36 (&lt;2.80)</td>
</tr>
<tr>
<td>2,3-position&lt;sup&gt;b&lt;/sup&gt;</td>
<td>———</td>
<td>———</td>
<td>———</td>
</tr>
<tr>
<td>3,4-position</td>
<td>−1.99 (&lt;1.81)</td>
<td>−2.34 (&lt;2.20)</td>
<td>−2.95 (&lt;2.80)</td>
</tr>
<tr>
<td>5,6-position</td>
<td>−1.13 (&lt;1.81)</td>
<td>−1.37 (&lt;2.20)</td>
<td>−1.81 (&lt;2.80)</td>
</tr>
<tr>
<td>6,7-position&lt;sup&gt;b&lt;/sup&gt;</td>
<td>———</td>
<td>———</td>
<td>———</td>
</tr>
<tr>
<td>7,8-position</td>
<td>−1.27 (&lt;1.81)</td>
<td>−1.57 (&lt;2.20)</td>
<td>−2.08 (&lt;2.80)</td>
</tr>
</tbody>
</table>

### 9-nitroanthracene

<table>
<thead>
<tr>
<th>Epoxidation position</th>
<th>Gas phase</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-position</td>
<td>−0.33 (&lt;1.81)</td>
<td>−0.55 (&lt;2.20)</td>
<td>−1.06 (&lt;2.80)</td>
</tr>
<tr>
<td>2,3-position&lt;sup&gt;b&lt;/sup&gt;</td>
<td>———</td>
<td>———</td>
<td>———</td>
</tr>
<tr>
<td>3,4-position</td>
<td>−0.89 (&lt;1.81)</td>
<td>−1.07 (&lt;2.20)</td>
<td>−1.44 (&lt;2.80)</td>
</tr>
</tbody>
</table>

<sup>a</sup> At the PCM(solvent)-B3LYP/6-31+G**//B3LYP(gas)/6-31G* level of theory.

<sup>b</sup> Geometry optimizations of the corresponding epoxides yielded oxepines instead of epoxides.

Table 4.3. Oxidation enthalpies (ΔH<sub>0</sub>, kcal/mol, B3LYP/6-31+G**//B3LYP/6-31G*) for the reactions of nitroanthracenes with hydroperoxyl radical (Figure 4.1) and comparison with the oxidation of anthracene (in parentheses).
For 1-nitroanthracene, two main trends are readily apparent: oxidation at the 5,6-position is the most thermodynamically favored, and the presence of the nitro group reduces the favorability of epoxidation, compared to anthracene alone, regardless of solvent. In 1-nitroanthracene, oxidation occurs on a ring which does not bear the nitro group. As opposed to 1-nitronaphthalene, for 2-nitroanthracene, the most favored position of epoxidation is the 3,4-position, which shares the same ring as the nitro group, regardless of solvation, and is slightly more favored than that of the parent compound. For 9-nitroanthracene, oxidation at the 1,2-position is 0.5 kcal/mol less favorable than oxidation at the 3,4-position. The regioselectivities of all three nitroanthracenes can be mainly attributed to the aromaticity preserved in the untouched naphthalene ring. In addition, electronic inductive effects may also play some roles in controlling these regioselectivities.

As with the smaller systems, the effect of solvent on these calculations was explored. It was again seen that increasing the dielectric constant of the solvent led to more complicated results than anthracene alone: the oxidation at the 1,2-position of 1-nitroanthracene and 2-nitroanthracene are less favorable since the $\Delta H_0$ is increased; the oxidation at the 3,4-position of 1-nitroanthracene is not affected; for the rest of the positions of each nitroanthracene isomer, they are more favorably oxidized. As was noted for the nitronaphthalenes, changing solvents had no effect on the overall regioselectivity preferences for the epoxidation of nitroanthracenes.
4.3.4 Nitrophenanthrene

The locants are labeled in Figure 4.6.

Figure 4.6. Nitrophenanthrene and its numbering.

Nitrophenanthrene exists in five isomeric forms: 1-, 2-, 3-, 4-, and 9-nitrophenanthrene. The oxidation enthalpies ($\Delta H_0$) of the nitrophenanthrene derivatives are listed in Table 4.4. The oxidation enthalpies ($\Delta H_0$) of the parent compound, phenanthrene, are listed for comparison.
### 1-nitrophenanthrene

<table>
<thead>
<tr>
<th>Epoxidation position</th>
<th>Gas phase</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-position</td>
<td>5.58 (5.45)</td>
<td>5.71 (2.56)</td>
<td>5.67 (−2.34)</td>
</tr>
<tr>
<td>2,3-position</td>
<td>16.93 (18.45)</td>
<td>16.66 (15.64)</td>
<td>16.24 (10.84)</td>
</tr>
<tr>
<td>3,4-position</td>
<td>7.40 (5.39)</td>
<td>7.35 (2.53)</td>
<td>7.23 (−2.34)</td>
</tr>
<tr>
<td>5,6-position</td>
<td>5.64 (5.39)</td>
<td>5.41 (2.53)</td>
<td>5.03 (−2.34)</td>
</tr>
<tr>
<td>6,7-position</td>
<td>18.76 (18.45)</td>
<td>18.55 (15.64)</td>
<td>18.25 (10.84)</td>
</tr>
<tr>
<td>7,8-position</td>
<td>5.69 (5.45)</td>
<td>5.40 (2.56)</td>
<td>4.95 (−2.34)</td>
</tr>
<tr>
<td>9,10-position</td>
<td>−2.74 (−3.85)</td>
<td>−2.73 (−6.75)</td>
<td>−2.79 (−11.73)</td>
</tr>
</tbody>
</table>

### 2-nitrophenanthrene

<table>
<thead>
<tr>
<th>Epoxidation position</th>
<th>Gas phase</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-position</td>
<td>7.49 (5.45)</td>
<td>7.83 (2.56)</td>
<td>8.21 (−2.34)</td>
</tr>
<tr>
<td>2,3-position</td>
<td>20.37 (18.45)</td>
<td>20.76 (15.64)</td>
<td>21.13 (10.84)</td>
</tr>
<tr>
<td>3,4-position</td>
<td>5.04 (5.39)</td>
<td>4.73 (2.53)</td>
<td>4.27 (−2.34)</td>
</tr>
<tr>
<td>5,6-position</td>
<td>5.65 (5.39)</td>
<td>5.34 (2.53)</td>
<td>4.84 (−2.34)</td>
</tr>
<tr>
<td>6,7-position</td>
<td>18.79 (18.45)</td>
<td>18.55 (15.64)</td>
<td>18.18 (10.84)</td>
</tr>
<tr>
<td>7,8-position</td>
<td>5.86 (5.45)</td>
<td>5.58 (2.56)</td>
<td>5.12 (−2.34)</td>
</tr>
<tr>
<td>9,10-position</td>
<td>−3.43 (−3.85)</td>
<td>−3.70 (−6.75)</td>
<td>−4.20 (−11.73)</td>
</tr>
</tbody>
</table>

### 3-nitrophenanthrene

<table>
<thead>
<tr>
<th>Epoxidation position</th>
<th>Gas phase</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-position</td>
<td>5.06 (5.45)</td>
<td>4.77 (2.56)</td>
<td>4.24 (−2.34)</td>
</tr>
<tr>
<td>2,3-position</td>
<td>20.59 (18.45)</td>
<td>20.95 (15.64)</td>
<td>21.33 (10.84)</td>
</tr>
<tr>
<td>3,4-position</td>
<td>7.45 (5.39)</td>
<td>7.81 (2.53)</td>
<td>8.28 (−2.34)</td>
</tr>
<tr>
<td>5,6-position</td>
<td>6.07 (5.39)</td>
<td>5.84 (2.53)</td>
<td>5.36 (−2.34)</td>
</tr>
<tr>
<td>6,7-position</td>
<td>18.70 (18.45)</td>
<td>18.42 (15.64)</td>
<td>17.96 (10.84)</td>
</tr>
<tr>
<td>7,8-position</td>
<td>5.94 (5.45)</td>
<td>5.67 (2.56)</td>
<td>5.19 (−2.34)</td>
</tr>
<tr>
<td>9,10-position</td>
<td>−2.90 (−3.85)</td>
<td>−2.99 (−6.75)</td>
<td>−3.27 (−11.73)</td>
</tr>
</tbody>
</table>

Table 4.4 Oxidation enthalpies ($\Delta H_0$, kcal/mol, B3LYP/6-31+G**//B3LYP/6-31G*) for the reactions of nitrophenanthrene with hydroperoxyl radical (Figure 4.1) and comparison with the oxidation of phenanthrene (in parentheses).

Table 4 is continued
Phenanthrene and nitrophenanthrene are angular polycyclic species, while naphthalene, anthracene and their nitro derivatives are linear. This fact leads to some heretofore unseen results.

In all of the nitrophenanthrene derivatives, as well as phenanthrene itself, the most favored position for epoxidation is the 9,10-position. This exclusive regioselectivity is attributed to the relative aromaticity of the potential products. When oxidation occurs

Table 4 (continued):

<table>
<thead>
<tr>
<th>Epoxidation position</th>
<th>4-nitrophenanthrene</th>
<th>9-nitrophenanthrene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gas phase</td>
<td>In benzene</td>
</tr>
<tr>
<td>1,2-position</td>
<td>5.70 (5.45)</td>
<td>5.50 (2.56)</td>
</tr>
<tr>
<td>2,3-position</td>
<td>19.90 (18.45)</td>
<td>19.98 (15.64)</td>
</tr>
<tr>
<td>3,4-position</td>
<td>1.55 (5.39)</td>
<td>1.64 (2.53)</td>
</tr>
<tr>
<td>5,6-position</td>
<td>5.98 (5.39)</td>
<td>5.41 (2.53)</td>
</tr>
<tr>
<td>6,7-position</td>
<td>17.86 (18.45)</td>
<td>17.64 (15.64)</td>
</tr>
<tr>
<td>7,8-position</td>
<td>5.07 (5.45)</td>
<td>4.58 (2.56)</td>
</tr>
<tr>
<td>9,10-position</td>
<td>−2.82 (−3.85)</td>
<td>−2.99 (−6.75)</td>
</tr>
</tbody>
</table>

<sup>a</sup> At the PCM(solvent)-B3LYP/6-31+G**/B3LYP(gas)/6-31G* level of theory.
across 2,3- and 6,7-position of nitrophenanthrene, only one benzene ring is preserved. When oxidation occurs across the 1,2-, 3,4-, 5,6- or 7,8-positions of nitrophenanthrene, the naphthalene moiety is preserved. When oxidation occurs across the 9,10-position, however, two benzene rings are preserved. This selectivity is consistent with the enhanced nucleophilic reactivity of the 9,10 double bond in numerous transformations.\textsuperscript{38,39} For all of the nitrophenanthrenes, except for the oxidation at 2,3-position of 1-nitrophenanthrene, oxidation at the 3,4-position of 2-nitrophenanthrene, oxidation at the 1,2-position of 3-nitrophenanthrene and oxidation at the 3,4-position, 6,7- and 7,8-position of 4-nitrophenanthrene in the gas phase and oxidation at 3,4-position of 4-nitrophenanthrene in benzene, the nitro group renders less favorable energetics for epoxidation, and regardless of solvation, when compared with phenanthrene.

Solvent effects on nitrophenanthrene oxidation are different from that on phenanthrene alone. In the condensed phase, as the dielectric constant of the solvent increases (moving from benzene to water), for some nitrophenanthrene derivatives, $\Delta H_0$ is slightly decreased and thus the oxidation is more favored; for others, $\Delta H_0$ is slightly increased which implies the oxidation in polar solvent is disfavored. But for phenanthrene alone, when the dielectric constant of the solvent increases, $\Delta H_0$ significantly decreases, thus, more polar solvents favor the oxidation of phenanthrene to a greater extent. Again, as with the previous compounds examined, the regioselectivity of the epoxidation does not vary with the solvation environment.
4.3.5 *Nitropyrene*

Locants on nitropyrene are labeled in Figure 4.7.

![Nitropyrene and its numbering.](image)

**Figure 4.7.** Nitropyrene and its numbering.

The nitropyrenes exist in three regioisomeric forms: 1-nitropyrene, 2-nitropyrene and 4-nitropyrene. All of the oxidation enthalpies ($\Delta H_0$) of 1-nitropyrene, 2-nitropyrene and 4-nitropyrene have been compiled in Table 4.5. Again, the oxidation enthalpies ($\Delta H_0$) of the parent compound, pyrene, are listed for comparison.
### 1-nitropyrene

<table>
<thead>
<tr>
<th>Epoxidation position</th>
<th>Gas phase</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-position</td>
<td>11.40 (10.56)</td>
<td>11.69 (10.24)</td>
<td>11.89 (9.74)</td>
</tr>
<tr>
<td>2,3-position</td>
<td>8.61 (10.56)</td>
<td>7.79 (10.24)</td>
<td>6.40 (9.74)</td>
</tr>
<tr>
<td>4,5-position</td>
<td>−3.04 (−4.59)</td>
<td>−3.07 (−4.93)</td>
<td>−3.20 (−5.48)</td>
</tr>
<tr>
<td>6,7-position</td>
<td>11.19 (10.56)</td>
<td>11.02 (10.24)</td>
<td>10.70 (9.74)</td>
</tr>
<tr>
<td>7,8-position</td>
<td>10.79 (10.56)</td>
<td>10.53 (10.24)</td>
<td>10.07 (9.74)</td>
</tr>
<tr>
<td>9,10-position</td>
<td>−2.98 (−4.59)</td>
<td>−2.86 (−4.93)</td>
<td>−2.72 (−5.48)</td>
</tr>
</tbody>
</table>

### 2-nitropyrene

<table>
<thead>
<tr>
<th>Epoxidation position</th>
<th>Gas phase</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-position</td>
<td>12.37 (10.56)</td>
<td>12.68 (10.24)</td>
<td>12.92 (9.74)</td>
</tr>
<tr>
<td>2,3-position</td>
<td>12.37 (10.56)</td>
<td>12.68 (10.24)</td>
<td>12.92 (9.74)</td>
</tr>
<tr>
<td>4,5-position</td>
<td>−4.21 (−4.59)</td>
<td>−4.46 (−4.93)</td>
<td>−4.92 (−5.48)</td>
</tr>
<tr>
<td>6,7-position</td>
<td>10.93 (10.56)</td>
<td>10.67 (10.24)</td>
<td>10.22 (9.74)</td>
</tr>
</tbody>
</table>

### 4-nitropyrene

<table>
<thead>
<tr>
<th>Epoxidation position</th>
<th>Gas phase</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-position</td>
<td>10.88 (10.56)</td>
<td>10.59 (10.24)</td>
<td>10.08 (9.74)</td>
</tr>
<tr>
<td>2,3-position</td>
<td>11.51 (10.56)</td>
<td>11.52 (10.24)</td>
<td>11.52 (9.74)</td>
</tr>
<tr>
<td>4,5-position</td>
<td>−3.82 (−4.59)</td>
<td>−3.70 (−4.93)</td>
<td>−3.70 (−5.48)</td>
</tr>
<tr>
<td>6,7-position</td>
<td>10.69 (10.56)</td>
<td>10.43 (10.24)</td>
<td>9.97 (9.74)</td>
</tr>
<tr>
<td>7,8-position</td>
<td>11.28 (10.56)</td>
<td>11.09 (10.24)</td>
<td>10.70 (9.74)</td>
</tr>
<tr>
<td>9,10-position</td>
<td>−3.90 (−4.59)</td>
<td>−4.13 (−4.93)</td>
<td>−4.55 (−5.48)</td>
</tr>
</tbody>
</table>

<sup>a</sup> At the PCM(solvent)-B3LYP/6-31+G**/B3LYP(gas)/6-31G* level of theory.

**Table 4.5.** Oxidation enthalpies ($\Delta H_0$, kcal/mol, B3LYP/6-31+G**/B3LYP/6-31G*) for the reactions of nitropyrene with hydroperoxyl radical (Figure 4.1) and comparison with the oxidation of pyrene (in parentheses).
For all three nitropyrene regioisomers, epoxidations at the 4,5- or 9,10-positions are the most thermodynamically favored. The regioselectivities can be mainly attributed to the aromaticity of the remaining phenanthrene ring when the 4,5-position or the 9,10-position is oxidized. Compared with the parent compound, pyrene, the oxidation capabilities of the nitropyrenes are reduced, except for the oxidation on the 2,3-position of 1-nitropyrene, regardless of the solvent. When the solvent’s polarity is changed from gas phase to benzene to water (i.e., the dielectric constant of the solvent increases) $\Delta H_0$ values for oxidation at the 1,2- and 9,10-position of 1-nitropyrene and oxidation at the 1,2- and 2,3-positions of 2-nitropyrene are increased; thus, a polar solvent disfavors the oxidation. For oxidation at the 2,3- and 4,5-positions of 4-nitropyrene, $\Delta H_0$ does not change significantly when the dielectric constant changes. For the rest, the oxidations are more favored when the dielectric constant of the solvent increases since $\Delta H_0$ is decreased; this is also seen with pyrene alone. As seen previously, solvent effects do not change the regioselectivity of epoxidation.

4.4 Conclusions

Our DFT studies of the epoxidations of NPAHs reveal that these processes are regioselective oxidations and that these regioselectivities are mainly attributed to the maximization of aromaticity and stability in the resulting epoxides (or rearranged oxepines). The NPAHs tend to react in such a manner as to maximize the remaining aromaticity. They tend to favor the preservation of two benzene rings over one naphthalene ring, one naphthalene ring over one benzene ring, and a benzene ring over three non-conjugated double bonds. In the condensed phase, the oxidations of the
NPAHs are complicated with increasing dielectric constants, while qualitative trends are preserved, and thus the regioselectivities are not affected by solvents. The presence of an electron-withdrawing nitro group has varying effects on the oxidation capability of an aromatic ring: for nitrobenzene, 2-nitronaphthalene, and 2-nitroanthracene, oxidation at the most favored position occurs more readily than oxidation of the parent PAH, while for the remaining NPAHs, the inductive effect of the nitro group does reduce the NPAH’s oxidation capability at the most favored position.

4.5 References


   (b) Onchoke, K. K.; Hadad, C. M.; Dutta, P. K. *Polycyclic Aromatic Compounds*, 2004, 24, 37-64.  


CHAPTER 5

COMPUTATIONAL EXPLORATIONS OF THE ISOMERIZATION OF ARENE OXIDES TO OXEPINES

5.1 Introduction

Polycyclic aromatic hydrocarbons (PAHs) result from incomplete combustion processes and are well-known environmental pollutants found both in urban and rural areas.\textsuperscript{1-6} Through metabolic activation, PAHs can be transformed to reactive intermediates, and these intermediates can react with biological molecules such as DNA; hence, PAHs are often carcinogenic and mutagenic.\textsuperscript{7-8} Three steps are needed to activate PAHs in biological systems,\textsuperscript{9-11} as shown in Figure 5.1.\textsuperscript{12} First, PAHs are catalytically oxidized by cytochrome P-450 monooxygenases to produce epoxides; second, epoxide hydrase (EH) enzyme-mediated hydrolysis converts the epoxides to the trans diols; third, epoxidation at the adjacent double bond yields a diol-epoxide which can then interact with nucleophilic DNA, giving rise to the alkylation of DNA and resulting in carcinogenicity and mutagenicity.\textsuperscript{12-14} This proposal has been widely accepted since 1968, when naphthalene-1,2-oxide, a metabolite of naphthalene, was isolated.\textsuperscript{15} In the process of epoxidation of PAHs, the oxygen atom is preferentially added to one
stereoheterotopic face of an aromatic ring by the monooxygenase enzyme to form the optically active arene oxides.\textsuperscript{16}

\textbf{Figure 5.1.} Metabolic activative pathways of PAH leading to the formation of diol-epoxide, a precursor of DNA adducts proposed by Borosky.\textsuperscript{12}

Since the subsequent enzyme-catalyzed reactions and biological activities of arene oxides are often dependent upon their absolute configuration, it is important to study the configurational stability of these optically active arene oxides. The initial epoxide (arene oxide) intermediates in biological systems are generally difficult to detect due to their propensity for side reactions (aromatization via formation of the corresponding phenols and facile ring-opening by various nucleophiles).\textsuperscript{17} In order to investigate the absolute configurational stability of arene oxides and their further reactions, several asymmetric syntheses of arene oxides have been developed.\textsuperscript{16} Studies on arene oxides derived from single enantiomer precursors have shown that their configurational stabilities vary with the structures of the PAHs. Some arene oxide enantiomers spontaneously racemize,\textsuperscript{18} while other arene oxides, such as phenanthrene-1,2-oxide and 3,4-oxide, were initially obtained in enantiopure form but were observed to racemize slowly at ambient temperature via undetected oxepine isomers.\textsuperscript{19-20} Some arene oxides are very stable in their optical activity, such as anthracene-1,2-oxide and
naphthalene-1,2-oxide. The racemization of enantiopure arene oxides results from the oxirane ring inversion between the two faces of the arene via an oxepine isomer as shown in Scheme 5.1.

**Scheme 5.1.** The most plausible mechanism for the racemization of arene oxides

First, the oxirane ring is opened to give the corresponding oxepine, then recloses to give either enantiomer of the arene oxide, resulting in racemization. However, many of the oxepine intermediates derived from PAHs are unstable, so this scheme may be difficult to verify experimentally. In order to discover the origin of the racemization, to find the configuration stability of optically active arene oxides and thus to better understand their biological activities, computational approaches provide an important tool. In seminal contributions, Boyd *et al.* have theoretically studied the isomerization of arene oxides by using perturbation methods with molecular orbital theory to calculate electronic energy differences between the stable isomers. Since density functional theory (DFT) calculations together with *ab initio* molecular orbital calculations have been successfully performed in a number of reaction systems to predict and rationalize many experimental results, we have used this computational method to examine the feasibility
and the facility of the isomerization of arene oxides on energetic grounds and to investigate the effect of structural changes and solvent changes on the energetics of isomerization. Herein, we report our computational results calculated at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level, in both the gas phase and with the PCM model for solvation (benzene and water). The free energies for both arene oxides and the corresponding oxepines were calculated, as well as the free energies for the isomerization $\Delta G^0_{\text{rxn}}(298K)$. The transition states for these mechanistic steps were also obtained, and the free energies of activation $\Delta G^\text{\#}(298K)$ were calculated. Solvent effects on the isomerization are also discussed, and when available, the results are compared with available experimental data and used to explain some of the experimental phenomena.

5.2 Computational Methods

Hybrid density functional theory (DFT)\(^{24}\) was employed in order to obtain optimized geometries and vibrational frequencies for all stationary points at the B3LYP/6-31G(d) levels of theory.\(^{25}\) Single-point energies in the gas phase were obtained at the B3LYP/6-31+G(d,p) level based on the optimized B3LYP/6-31G(d) geometries. The effect of solvation was investigated with the polarizable continuum model (PCM) for both benzene and water with single-point energy calculations at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level.\(^{26}\) All calculations were performed with Gaussian 03.\(^{27}\)

Stationary points were confirmed to be minima for both isomers, epoxides and oxepines, via vibrational frequency analyses at the B3LYP/6-31G(d) levels of theory. The optimized transition-state structures were confirmed to have one imaginary
vibrational frequency and, furthermore, were shown to be connected to the desired reactant and product by displacement along the normal coordinate (typically 10%) for the imaginary vibrational frequency in the positive and negative directions, followed by careful minimization (opt = calcfc). Hence, each of the epoxides and oxepines reported here is the result of complete geometry optimization after displacement of the TS structure along the reaction coordinate.

A scaling factor of 0.9806 was used for the zero-point vibrational energy (ZPE) corrections for the B3LYP/6-31G(d) geometries.\textsuperscript{28} Thermal corrections were used to convert electronic energies to the thermodynamic quantities of interest at 298 K. Reaction and activation enthalpies followed the same trends as free energies of reaction and free energies of activation. For the sake of simplicity, we will confine our discussion to the $\Delta G_{\text{rxn}}^0(298\text{K})$ and $\Delta G^\circ(298\text{K})$ values for the reactions of interest. All enthalpies and free energies are included in the Supporting Information.

5.3 Results and discussion

This study evaluated arene oxides derived from benzene, naphthalene, anthracene, phenanthrene, and pyrene, as shown in Figure 5.2. Benzene epoxide is the simplest arene oxide. Aside from benzene oxide, several regioisomers can plausibly be derived from each PAH.
Figure 5.2. Atomic numbering for benzene, naphthalene, anthracene, phenanthrene and pyrene.

Structures for the PAH derivatives are shown in Table 5.1 with the bond distances [R(C–C)] between the two carbons which bond to the oxygen, for the calculations that completed successfully. Not all geometries were successfully optimized; the oxepine isomers of naphthalene-1,2-oxide, phenanthrene-9,10-oxide, and pyrene-4,5-oxide could not be computed, and neither could the transition state involved in the isomerization of anthracene-1,2-epoxide. Finally, attempts to optimize anthracene-2,3-epoxide always returned oxepine as reported earlier.29
<table>
<thead>
<tr>
<th>Parent PAH</th>
<th>Epoxide</th>
<th>Transition state</th>
<th>Oxepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td><img src="image1" alt="Benzene Epoxide" /></td>
<td><img src="image2" alt="Benzene Transition State" /></td>
<td><img src="image3" alt="Benzene Oxepine" /></td>
</tr>
<tr>
<td>R(C−C), Å</td>
<td>1.52</td>
<td>1.85</td>
<td>2.31</td>
</tr>
<tr>
<td>Naphthalene 2,3-</td>
<td><img src="image4" alt="Naphthalene 2,3-Epoxide" /></td>
<td><img src="image5" alt="Naphthalene 2,3-Transition State" /></td>
<td><img src="image6" alt="Naphthalene 2,3-Oxepine" /></td>
</tr>
<tr>
<td>R(C−C), Å</td>
<td>1.56</td>
<td>1.69</td>
<td>2.42</td>
</tr>
<tr>
<td>Pyrene 1,2-</td>
<td><img src="image7" alt="Pyrene 1,2-Epoxide" /></td>
<td><img src="image8" alt="Pyrene 1,2-Transition State" /></td>
<td><img src="image9" alt="Pyrene 1,2-Oxepine" /></td>
</tr>
<tr>
<td>R(C−C), Å</td>
<td>1.50</td>
<td>1.90</td>
<td>2.36</td>
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<tr>
<td>Phenanthrene 1,2-</td>
<td><img src="image10" alt="Phenanthrene 1,2-Epoxide" /></td>
<td><img src="image11" alt="Phenanthrene 1,2-Transition State" /></td>
<td><img src="image12" alt="Phenanthrene 1,2-Oxepine" /></td>
</tr>
<tr>
<td>R(C−C), Å</td>
<td>1.50</td>
<td>2.00</td>
<td>2.22</td>
</tr>
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**Table 5.1.** Geometries of the oxides (reactants), transition state (TSs) and oxepines (products) of the interested PAHs, optimized at the B3LYP/6-31G(d) level in gas phase. The corresponding distance (Å) between the two carbon atoms which bond to the oxygen atom [R(C−C)] is given below each structure.

Table 5.1 is continued
As a given isomerization reaction progresses, the distance between the two carbons of the oxirane ring becomes larger and larger. Eventually, the bond between these two carbons is broken, and the epoxide isomerizes to the oxepine. As shown in Table 5.1, in the arene oxides, all of the carbons are nearly coplanar and the carbon-carbon bond distances in the oxiranes are ~1.50 Å. For the oxepine products, the distance between these two carbons is much larger, widely ranging from 2.22 – 2.42 Å. When the aromaticity exists in the adjacent ring of the oxepine ring, the distance between these two carbons tends to be longer in order for these two carbons to remain coplanar with the rest of the carbons in the molecule, and for the carbon-carbon double bonds in the oxepine ring to conjugate effectively with the adjacent ring. This can be seen in the oxepines generated from naphthalene-2,3-epoxide, from pyrene-1,2-oxide and from phenanthrene-2,3-oxide in Table 5.1. For the oxepines derived from benzene oxide, phenanthrene-1,2-
oxide and phenanthrene-3,4-oxide, in which the adjacent ring can not be aromatic, the distance between these two carbons is shorter and the two carbons tend not to be coplanar with the rest of the carbons in the molecule, thus preventing the oxepine ring from any antiaromatic character.

The energetic nature of a given isomerization reaction can be discerned from the geometric information involved. According to Hammond’s postulate, if a transition state resembles its reactant, then the reaction is exothermic; if a transition state resembles the product, then the reaction is endothermic. The transition states we examined can be compared to both their corresponding reactants and products. For example, R(C\(-\)C) in the transition state for the isomerization of phenanthrene-2,3-oxide is 1.74 Å, closer to the R(C\(-\)C) value in the reactant epoxide (1.53 Å) than in the oxepine (2.35 Å) product; thus the transition state is formed early along the reaction coordinate, and the reaction should be exothermic. Conversely, the isomerization of the phenanthrene-3,4-oxide involves a transition state in which the R(C\(-\)C) value is 2.00 Å, closer to the R(C\(-\)C) value of the product oxepine than the reactant epoxide; this reaction demonstrates a late transition state so this reaction would be endothermic. We verified these conclusions via a comprehensive look at the energies of reaction (Table 5.2).

We completed this comprehensive examination (Table 5.2) in both gas-phase and condensed-phase evaluations. Single-point energy calculations were performed at the B3LYP/6-31+G(d,p) level for the gas phase and with the polarizable continuum model (PCM) at the single-point B3LYP/6-31+G(d,p) level of theory for solvation in benzene and water based on the optimized gas-phase geometries. In terms of the Gibbs free energy of reaction \( \Delta G_{\text{rxn}}^0(298\text{K}) \), a negative value indicates that the forward
isomerization (epoxide to oxepine) is favored and the corresponding oxepine is thermodynamically the major isomer; a positive value shows that the forward isomerization is disfavored and the epoxide is thermodynamically predicted to be the major isomer. The free energy of activation \([\Delta G^\neq(298K)]\) determines the facility of the isomerization: the isomerization is fast when the free energy of activation is small; the isomerization is slow when the free energy of activation is large.

<table>
<thead>
<tr>
<th>Arene Oxide</th>
<th>Gas phase</th>
<th>Benzene(^c)</th>
<th>Water(^c)</th>
</tr>
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<tr>
<td></td>
<td>(\Delta G^g)</td>
<td>(\Delta G^\text{rxn})</td>
<td>(\Delta G^g)</td>
</tr>
<tr>
<td>Benzene-1,2-</td>
<td>4.87</td>
<td>-2.20</td>
<td>5.12</td>
</tr>
<tr>
<td>Naphthalene-1,2-(^a)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Naphthalene-2,3-</td>
<td>0.01</td>
<td>-21.08</td>
<td>0.16</td>
</tr>
<tr>
<td>Anthracene-1,2-(^a)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Anthracene-2,3-(^b)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Pyrene-1,2-</td>
<td>9.66</td>
<td>3.20</td>
<td>9.98</td>
</tr>
<tr>
<td>Pyrene-4,5-(^a)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Phenanthrene-2,3-</td>
<td>1.39</td>
<td>-13.28</td>
<td>1.61</td>
</tr>
<tr>
<td>Phenanthrene-9,10-(^a)</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

\(^a\) Geometry of the oxepine or the transition state could not be computed, despite repeated attempts.
\(^b\) Geometry optimization of the corresponding epoxide gave an oxepine instead.
\(^c\) The PCM(solvent)-B3LYP/6-31+G(d,p)//B3LYP(gas)/6-31G(d) level of theory.

**Table 5.2.** Free energies of reaction \([\Delta G^\text{rxn}(298K)]\) and free energies of activation \([\Delta G^\neq(298K)]\) (kcal/mol) for the isomerization of arene oxides to the corresponding oxepines in the gas phase, benzene and water, calculated at the B3LYP/6-31+G(d,p)//B3LYP(gas)/6-31G(d) level of theory.
As noted in Table 5.2, since some geometries could not be optimized, the isomerization data related to these compounds are not shown. From Table 5.2, the isomerization free energies of phenanthrene-2,3-oxide and naphthalene-2,3-oxide are very exoergic. The exoergicity can be mainly attributed to the increase in aromaticity after the isomerization to the oxepine. As shown in Figure 5.3, there is no aromaticity in naphthalene-2,3-oxide, but there is an intact aromatic benzene ring in the oxepine isomer derived from this epoxide. For phenanthrene-2,3-oxide, there is aromaticity from one benzene ring, but the oxepine isomer, on the other hand, retains aromaticity of a naphthalene unit. So the aromaticities in the oxepine isomers are more significant than in the epoxide isomers; thus, the corresponding oxepines are the favored valence tautomers.

For both species, isomerization occurs quickly since the free energies of activation are small, with $\Delta G^\ddagger(298K) = 0.01$ and 1.39 kcal/mol for the isomerization of naphthalene-2,3-oxide and phenanthrene-2,3-oxide, respectively. The facileness of the isomerization and the strong preference of the oxepines can explain why naphthalene-2,3-oxide and phenanthrene-2,3-oxide have not been detected. From the color changes due to the

**Figure 5.3.** Isomerization of naphthalene-2,3-oxide (top) and phenanthrene-2,3-oxide (bottom) to the corresponding oxepines.
different isomers, some authors have determined that benzene oxide and the oxepine coexist; hence, the energy difference between the isomers must be small (< 3 kcal/mol).\textsuperscript{30} From the calculated results listed in the Table 5.2, the free energy of activation is small (4.87 kcal/mol) and the free energy of reaction is small (~2.20 kcal/mol in gas phase), too; thus, the epoxide and the oxepine are both thermodynamically stable and exchangeable at room temperature. For the isomerizations of phenanthrene-3,4-oxide and phenanthrene-1,2-oxide, one aromatic ring is ‘lost’ over the course of the reaction, as the epoxides each contain a naphthalene system and the oxepines have only a benzene ring; thus, the free energies of reaction are rather positive (13.12 and 12.56 kcal/mol, respectively), and the dominant component at equilibrium is the epoxide. The free energies of activation for phenanthrene-3,4-oxide and phenanthrene-1,2-oxide are 14.59 and 13.50 kcal/mol, respectively, so the isomerization is slow but can occur at room temperature. For the isomerization of pyrene-1,2-oxide, the aromaticity does not change and the free energy of reaction and the free energy of activation are relatively small (3.2 kcal/mol and 9.66 kcal/mol, respectively); the isomerization can occur easily at room temperature and the epoxide is more favored than the oxepine.

As noted in the introduction, racemization of an optically active arene oxide results from the isomerization of the arene oxide to the corresponding oxepine, followed by the reclosure of the oxepine to give either enantiomer of the arene oxide (see Scheme 5.1). The faster the isomerization of arene oxides to oxepines, the more rapid will be the racemization of the optically active arene oxides. Therefore, when the activation free energy of isomerization is smaller, racemization is faster, and the absolute configuration of the optically active arene oxide is less stable. Conversely, when the activation free
energy is bigger, the racemization is slower, and the absolute configuration of the optically active arene oxide is more stable. The results in Table 5.2 are consistent with the available experimental observations. Naphthalene-1,2-oxide and anthracene-1,2-oxide are configurationally stable at ambient temperature. In these cases, we were unable to identify geometries for the corresponding oxepines, because they were so relatively unstable and highly energetic. Similarly, phenanthrene-1,2-oxide and -3,4-oxide are observed to racemize slowly at ambient temperature via undetected oxepine isomers. Our calculations showed that these racemizations would demonstrate substantial barriers to isomerization at 298 K: 13.50 kcal/mol for phenanthrene-1,2-oxide and 14.59 kcal/mol for phenanthrene-3,4-oxide. Finally, the oxepine isomers of phenanthrene-1,2-oxide and phenanthrene-3,4-oxide have not been detected, and these results are consistent with their free energies of reaction: 12.56 and 13.12 kcal/mol, respectively; thus, equilibrium favors the epoxide isomers to a significant extent.

In terms of solvation effects, as the dielectric constant of the solvent increases (from the gas phase to benzene to water), all of the free energies of isomerization increase, which implies that isomerization of the epoxides becomes less favorable; similarly, all of the free energies of activation also increase, implying that the rate for isomerization becomes slower. Thus, the epoxides are relatively more stable in solvents with a greater dielectric constant. However, relative to the gas phase, no significant qualitative changes to the favored isomers in each reaction were seen in the models of the condensed phases. All of the preceding results are summarized in Table 5.2.
5.4 Conclusions

In this work, we explored the isomerization of arene oxides derived from benzene and several PAHs to their corresponding oxepines, using DFT and PCM calculations. Our calculated results demonstrate the facility and the feasibility of the isomerization at room temperature on energetic grounds both from geometric information and Gibbs free energies. The results also reveal the effect of aromaticity on the energetics of the isomerization: when aromaticity increases during the isomerization, the forward reaction is favored both kinetically and thermodynamically; when aromaticity decreases, the isomerization is disfavored. The calculations elucidate the origin of the racemization of the optically active arene oxides: the larger the free energies of activation are, the more stable the absolute configuration of the optically active arene oxides; the smaller the free energies of activation are, the more unstable the absolute configuration. Our results were found to be consistent with the available experimental observations. The solvent effects reveal that in solvents with a higher dielectric constant, isomerization is both thermodynamically and kinetically less favored and thus the absolute configurations of the optically active arene oxides are more stable.

5.5 References


CHAPTER 6

COMPUTATIONAL EXPLORATIONS OF THE ISOMERIZATION OF NITRATED ARENE OXIDES TO OXEPINES

6.1 Introduction

Nitration polycyclic aromatic hydrocarbons (NPAHs), well-known environmental pollutants, constitute an important class of polycyclic aromatic hydrocarbons (PAHs). While some NPAHs and PAHs usually result from incomplete combustion processes, such as emission from diesel combustion, NPAHs can also be formed by the reactions of parent PAHs with reactive nitrogen-containing species existing in the atmosphere. NPAHs are found both in urban and rural areas. Although the concentrations of NPAHs are somewhat lower than those of their parent PAHs, some NPAHs have been found to have higher toxicity than their parent PAHs. Consequently, this class of chemical carcinogens has attracted increasing attention in recent years.

Both PAHs and NPAHs generally exert their biological activity through metabolic activation which produces reactive intermediates that react with biological molecules, especially DNA. The presence of their nitro groups makes the metabolism of NPAHs more complicated: in addition to ring oxidation for PAHs, NPAHs may undergo reduction of the nitro group, or a combination of ring oxidation and nitro reduction.
nitro-reduction of NPAHs has been systematically studied both experimentally and theoretically by several groups,\textsuperscript{25,26} while less attention has been paid to the ring oxidation of NPAHs. In a plausible oxidation pathway, three steps are needed to activate NPAHs and PAHs to ultimately form carcinogens:\textsuperscript{27-29} first, cytochrome P-450 monooxygenase-mediated epoxidation; second, epoxide hydrase enzyme-catalyzed ring-epoxiding of the resultant epoxide to a trans diol; third, a second epoxidation of the adjacent double bond.\textsuperscript{30} The generated diol-epoxide can interact with DNA, leading to alkylated DNA and resulting in carcinogenicity and mutagenicity.\textsuperscript{30-32} For the first epoxidation, two issues have to be taken into account, i.e., regioselectivity and enantioselectivity. The Hadad group has thoroughly explored the regioselective epoxidation of both PAHs and NPAHs by computational studies, and the results were consistent with available experiment data.\textsuperscript{33,34} For the enantioselective epoxidation, the oxygen atom is preferentially added to one stereoheterotopic face of an aromatic ring by the monooxygenase enzyme to form the optically active arene oxides.\textsuperscript{35} The further enzyme-catalyzed reactions and the biological activities of NPAHs and PAHs depend on the absolute configuration of the arene oxides. Several experiments have been conducted to study the enantioselective epoxidation of PAHs.\textsuperscript{35} This work found that some optically active arene oxides obtained from enantiopure precursors are spontaneously racemized at room temperature. A proposed mechanism for the racemization of enantiopure arene oxides is shown in Scheme 6.1.\textsuperscript{36}
First, the oxirane ring is opened to give the corresponding seven-membered ring oxepine; then the oxepine re-closes to give either enantiomer of the arene oxide. In another words, it is this isomerization between arene oxides and oxepines that results in racemization and configuration instability. The isomerization of an arene oxide to the corresponding oxepine has been found for many arene oxides and nitroarene oxides; however, since many oxepine intermediates are unstable and have not been detected in the PAH and NPAH series,\textsuperscript{36} it is difficult to experimentally study these reactions.

In previous efforts,\textsuperscript{37} we used computational approaches to study the isomerization of arene oxides derived from PAHs at the B3LYP/6-31+G**//B3LYP/6-31G* level in both the gas phase and with the PCM model for solvation, in order to discover the origin of the racemization of PAH epoxides and thus better understand their biological activities. The results were found to be consistent with the available experimental observations. Given our ongoing interests in NPAHs, we would like to extend this approach (B3LYP/6-31+G**//B3LYP/6-31G* in the gas phase and with the PCM model for solvation) to explore the origin of the racemization of arene oxides derived from NPAHs. While NPAHs exhibit greater toxicity and mutagenicity than the
parent PAHs, it is unclear if the nitro substitution affects the isomerization between the corresponding epoxides and oxepines. Herein, we report our computational results on the isomerization of NPAH oxides to the corresponding oxepines. The free energies, $\Delta G^0_{\text{rxn}}(298K)$, for the isomerization between the nitroarene oxides and oxepines were calculated, and the transition states, along with the resulting free energies of activation, $\Delta G^\ddagger(298K)$, were also evaluated. The results are compared with the parent arene oxides and the effect of the nitro group on the isomerization and thus on the configurational stability of the epoxides was explored. Solvent effects on the isomerization were also examined.

### 6.2 Computational Methods

Hybrid density functional theory (DFT)\textsuperscript{38} was employed in order to obtain optimized geometries and vibrational frequencies for all stationary points at the B3LYP/6-31G(d) levels of theory.\textsuperscript{39} Single-point energies in the gas phase were obtained at the B3LYP/6-31+G(d,p) level, based on the optimized B3LYP/6-31G(d) geometries. The effect of solvation was investigated using the polarizable continuum model (PCM) for both water and benzene with single-point energy calculations at the B3LYP/6-31+G(d,p)/B3LYP(gas)/6-31G(d) level of theory.\textsuperscript{40} All calculations were performed with Gaussian 03.\textsuperscript{41}

Stationary points were confirmed to be minima via vibrational frequency analyses at the B3LYP/6-31G(d) levels of theory. The optimized transition state structures were confirmed to have one imaginary vibrational frequency and, furthermore, were shown to be connected to the desired reactant and product by displacement along the normal
coordinate (typically 10%) for the imaginary vibrational frequency in the positive and negative directions, followed by careful minimization (opt = calcfc).

A scaling factor of 0.9806 was used for the zero-point vibrational energy (ZPE) corrections for the B3LYP/6-31G(d) geometries. Thermal and entropic corrections, using unscaled vibrational frequencies, were used to convert electronic energies to the thermodynamic quantities of interest at 298 K. Reaction and activation enthalpies followed the same trends as free energies of reaction and activation. For the sake of simplicity, we will confine our discussion to the $\Delta G^0_{\text{rxn}}(298\text{K})$ and $\Delta G^\neq(298\text{K})$ values for the reactions of interest. All enthalpies and free energies are included in the Supporting Information.

6.3 Results and Discussion

This study explored the isomerization of nitro-arene oxides derived from nitrobenzene, nitronaphthalene, nitroanthracene, nitrophenanthrene and nitropyrene. The structures of these NPAHs are shown in Figure 6.1. Because the nitro group and oxirane can be located in different positions, several regioisomeric epoxides can be derived from each NPAH.
6.3.1 *Nitrobenzene*

We will first discuss the isomerization results obtained for the nitrobenzene epoxide, before turning our attention to the larger systems that govern much of NPAH chemistry. Epoxides derived from nitrobenzene can be located at three chemically distinct sites in the benzene ring: nitrobenzene-1,2-oxide, nitrobenzene-2,3-oxide, and nitrobenzene-3,4-oxide. Thus, the isomerizations of these three epoxides to the three corresponding oxepines were investigated. Selected data regarding the optimized structures of the epoxides, the oxepines, and the relevant transition states are shown in Table 6.1.
<table>
<thead>
<tr>
<th>Arene Oxide</th>
<th>Epoxide</th>
<th>Transition state</th>
<th>Oxepine</th>
</tr>
</thead>
<tbody>
<tr>
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<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
</tr>
<tr>
<td>R(C−C), Å</td>
<td>1.52</td>
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<td>2.27</td>
</tr>
<tr>
<td>Nitrobenzene-2,3-</td>
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<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
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<tr>
<td>R(C−C), Å</td>
<td>1.52</td>
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<td>2.35</td>
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<tr>
<td>Nitrobenzene-3,4-</td>
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<tr>
<td>R(C−C), Å</td>
<td>1.52</td>
<td>1.84</td>
<td>2.33</td>
</tr>
</tbody>
</table>

**Table 6.1.** Geometries of the oxides (reactants), transition states (TSs) and oxepines (products) of nitrobenzene, optimized at the B3LYP/6-31G(d) level in the gas phase. The corresponding distance between two carbon atoms which are bonded to oxygen (R(C−C), Å) is given below each structure.

As a given isomerization reaction progresses, the distance between the two carbons, R(C−C), of the oxirane ring becomes larger and larger. Eventually, the bond between these two carbons is broken and the epoxide isomerizes to the seven-membered ring oxepine. This observation is also true for the isomerization of other NPAH oxides. As shown in Table 6.1, the distance between the two carbons in the oxirane for each regioisomer of nitrobenzene oxide is the same (1.52 Å). For the transition states, the
distances become larger, \( \approx 1.84 \text{ Å} \), with a small increase in the distance for nitrobenzene-2,3-oxide. The C–C distances are much larger in the oxepines (\( \approx 2.3 \text{ Å} \)) than in the epoxides.

The energetic nature of a given isomerization reaction can be discerned from the geometric information involved. According to Hammond’s postulate, if a transition state resembles its reactant, then the reaction is exothermic; if a transition state resembles the product, then the reaction is endothermic. The transition states we examined can be compared to both their corresponding reactants and products. The carbon-carbon bond lengths \([R(C–C)]\) of interest in the transition states of the isomerization for each nitrobenzene oxide are nearly “halfway between” those of the epoxides and oxepines, indicating the reaction is neither very endothermic nor very exothermic. We verified these conclusions by consideration of the energies of reaction. We completed this examination (Table 6.2) using both gas-phase and condensed-phase conditions. Single-point energy calculations were performed based on the optimized geometries at the B3LYP/6-31+G(d,p) level for the gas phase and the polarizable continuum model (PCM) with B3LYP/6-31+G(d,p) level of theory for solvation in benzene and water. In terms of the Gibbs free energy of reaction \( \Delta G^{\text{rxn}}(298\text{K}) \), a negative value indicates that the isomerization from epoxide to oxepine is favored and the corresponding oxepine is thermodynamically the major isomer; a positive value shows that the forward isomerization is disfavored and the epoxide is thermodynamically the major isomer. The free energy of activation, \( \Delta G^\ddagger(298\text{K}) \), determines the facility of the isomerization: the isomerization is fast when the free energy of activation is small; conversely, the isomerization is slow when the free energy of activation is large. In Table 6.2, the
corresponding thermodynamic quantities for the isomerization of the parent benzene oxide are listed in parentheses for comparison.

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>Gas phase</th>
<th>Benzene$^a$</th>
<th>Water$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta G^\ne$</td>
<td>$\Delta G^\ne_{\text{rxn}}$</td>
<td>$\Delta G^\ne$</td>
</tr>
<tr>
<td>1,2-</td>
<td>4.99 (4.87)</td>
<td>-2.06 ($-2.20$)</td>
<td>4.90 (5.12)</td>
</tr>
<tr>
<td>2,3-</td>
<td>5.97 (4.87)</td>
<td>0.04 ($-2.20$)</td>
<td>6.32 (5.12)</td>
</tr>
<tr>
<td>3,4-</td>
<td>4.10 (4.87)</td>
<td>-3.55 ($-2.20$)</td>
<td>4.09 (5.12)</td>
</tr>
</tbody>
</table>

$^a$ At the PCM(solvent)-B3LYP/6-31+G(d,p)//B3LYP(gas)/6-31G(d) level of theory.

Table 6.2. Free energies of reaction [$\Delta G^\ne_{\text{rxn}}$(298K)] and free energies of activation [$\Delta G^\ne$(298K)] (kcal/mol) for the isomerization of nitrobenzene epoxides to the corresponding oxepines calculated at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level of theory, and comparison with the isomerization of benzene oxide (in parentheses).

As shown in Table 6.2, in the gas phase, the magnitude of the free energies of the isomerization for all three nitrobenzene epoxides are small, which is consistent with the conclusion obtained from Table 6.1: the reactions are neither very endoergic nor very exoergic. For the isomerization of nitrobenzene-3,4-epoxide, both the free energy of reaction and activation are the smallest; thus, the isomerization is the fastest and is the most complete. On the other hand, the isomerization of nitrobenzene-2,3-epoxide is both thermodynamically and kinetically the most unfavored. In the condensed phase, the effect of solvation on the isomerization of nitrated benzene oxides is complicated. When the dielectric constant increases (from the gas phase to benzene to water), for nitrobenzene-
1,2-oxide, both free energies of reaction and activation decrease in magnitude. Consequently, the isomerization occurs more easily and the corresponding oxepine is more favored. However, for nitrobenzene-2,3-oxide, the trend is reversed: the isomerization is more difficult, both thermodynamically and kinetically, when the dielectric constant of the solvent increases. For nitrobenzene-3,4-oxide, a different trend is evident: the free energy of reaction becomes more positive, while the free energy of activation almost remains the same, which means the epoxide becomes more favored thermodynamically, but the rate of the isomerization does not change with the increase of the dielectric constant. Compared with the parent arene oxide, the isomerization of nitrobenzene-3,4-oxide is both thermodynamically and kinetically more favored, since both the $\Delta G^0_{\text{rxn}}(298\text{K})$ and $\Delta G^\neq(298\text{K})$ are lower than those for benzene oxide, regardless of the change of the dielectric constant. On the other hand, the isomerization of nitrobenzene-2,3-oxide is both thermodynamically and kinetically less favored than that of the benzene oxide. When the isomerization of nitrobenzene-1,2-oxide is compared with the isomerization of benzene oxide in the gas phase, the isomerization of nitrobenzene-1,2-oxide is more difficult both thermodynamically and kinetically, but when the solvent is changed from the gas phase to benzene or water, this isomerization becomes faster and more feasible than the isomerization of benzene oxide.

6.3.2 Nitronaphthalene

Two isomers, 1-nitronaphthalene and 2-nitronaphthalene, exist for nitronaphthalene, and there are six potential regioisomeric epoxides for each nitronaphthalene. For the 1,2-, 3,4-, 5,6-, and 7,8-epoxides derived from both 1-nitro and 2-nitronaphthalene, the free energies of reaction [$\Delta G^0_{\text{rxn}}(298\text{K})$] and activation
[ΔG° (298K)] are not available because the corresponding oxepines are very unstable and the structures could not be optimized. This instability is mainly attributed to the disappearance of any aromaticity in the oxepines. The calculated isomerization free energies and the activation barriers for the rest of the oxides in the gas phase, benzene, and water are listed in Table 6.3. The corresponding thermodynamic quantities for the isomerization of the parent oxides (without a nitro group) are listed in parentheses for comparison.

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>Gas phase</th>
<th>Benzene (^a)</th>
<th>Water (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,3-</td>
<td>0.35 (0.01)</td>
<td>-15.55 (-21.08)</td>
<td>0.53 (0.16)</td>
</tr>
<tr>
<td>3,4-(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,6-(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6,7-</td>
<td>-0.15 (0.01)</td>
<td>-19.04 (-21.08)</td>
<td>-0.06 (0.16)</td>
</tr>
<tr>
<td>7,8-(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>Gas phase</th>
<th>Benzene (^a)</th>
<th>Water (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,3-</td>
<td>0.18 (0.01)</td>
<td>-19.86 (-21.08)</td>
<td>0.18 (0.16)</td>
</tr>
<tr>
<td>3,4-(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,6-(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6,7-</td>
<td>-0.07 (0.01)</td>
<td>-21.30 (-21.08)</td>
<td>0.02 (0.16)</td>
</tr>
<tr>
<td>7,8-(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) At the PCM(solvent)-B3LYP/6-31+G(d,p)//B3LYP(gas)/6-31G(d) level of theory.  
\(^b\) Unable to optimize the corresponding oxepines

**Table 6.3.** Free energies of reaction [ΔG° \(_{\text{rxn}}\) (298K)] and free energies of activation [ΔG\(^\varphi\) (298K)] (kcal/mol) for the isomerization of nitronaphthalene epoxides to the corresponding oxepines calculated at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level of theory, and comparison with the isomerization of naphthalene oxides (in parentheses).
For the isomerizations reported in Table 6.3, all of the available free energies of activation are close to zero, and all of the available free energies of reactions are very negative. Therefore, the isomerizations are both thermodynamically and kinetically very favored regardless of solvation. The exoergicity can be mainly attributed to the increase in the aromaticity after the isomerization. There is no aromaticity in the 2,3-oxide and 6,7-oxide derived from both 1-nitronaphthalene and 2-nitronaphthalene, but there is an aromatic benzene ring in the product oxepines. The favored valence tautomers are the corresponding oxepines. Although no significant qualitative changes to the favored isomers in each reaction were seen in the condensed phase relative to the gas phase, the increase of the dielectric constant (from gas phase to benzene to water) thermodynamically and kinetically disfavors the isomerization of 2,3- and 6,7-oxides derived from 1-nitronaphthalene and 6,7-oxide derived from 2-nitronaphthalene, since both the free energies of reaction and free energies of activation grow more positive. But for the isomerization of 2,3-oxide derived from 2-nitronaphthalene, the free energy of activation does not significantly change and the free energy of reaction decreases when the dielectric constant increases. Therefore the facility of the isomerization remains unchanged and the feasibility of the isomerization is increased. Compared with naphthalene-2,3-oxide, the parent arene oxide, the isomerization of 1-nitronaphthalene-2,3-oxide is slower and less favored to the oxepine isomer; the isomerization of 1-nitronaphthalene-6,7-oxide is kinetically more favored and thermodynamically less favored; the isomerization of 2-nitronaphthalene-6,7-oxide is both kinetically and thermodynamically more favored. However, the isomerization of 2-nitronaphthalene-2,3-oxide is complicated: if the isomerization occurs in the gas phase and benzene, the
reaction is less favored both kinetically and thermodynamically; when the solvent is water, the isomerization is more favored both kinetically and thermodynamically than the isomerization of the parent arene oxide.

### 6.3.3 Nitroanthracene

Theoretically, nitroanthracene exists in three isomeric forms: 1-nitroanthracene, 2-nitroanthracene and 9-nitroanthracene. There are six potential epoxide isomers for each of the nitroanthracenes. For the 1,2-, 3,4-, 5,6-, and 7,8-epoxides derived from each nitroanthracene isomer, the aromaticity originally in the naphthalene ring disappears during the isomerization, and thus the energies of the corresponding oxepines are too high for successful optimizations. For the 2,3- and 6,7-epoxides derived from each nitrated anthracene, the geometry optimization always gave an aromatic oxepine instead, a much more stable isomer with the aromaticity from an aromatic naphthalene ring. Therefore the free energies of reaction \([\Delta G^0_{\text{rxn}}(298\text{K})]\) and the free energy of activation barriers \([\Delta G^{\ddagger}(298\text{K})]\) for isomerization of any of the theoretically possible epoxides to the oxepines could not be obtained.

### 6.3.4 Nitrophenanthrene

Nitrophenanthrene exists in five isomeric forms: 1-nitrophenanthrene, 2-nitrophenanthrene, 3-nitrophenanthrene, 4-nitrophenanthrene, and 9-nitrophenanthrene. The 1,2-, 2,3-, 3,4-, 5,6-, 6,7-, 7,8-, and 9,10-epoxides are possible epoxides for each nitrophenanthrene regioisomer. For the 9,10-epoxide derived from any of the nitrophenanthrene isomers, the aromaticity from the two benzene ring disappears after
isomerization, and the corresponding oxepine is so unstable that the structure of the oxepine could not be optimized. The calculated free energies of reaction $[\Delta G^{0}_{\text{rxn}}(298K)]$ and the free energy of activation barriers $[\Delta G^{\neq}(298K)]$ in the gas phase, benzene, and water for the isomerization of the other epoxides are listed in Table 6.4. The corresponding thermodynamic quantities for the isomerizations of the parent oxides to the oxepines are listed in parentheses for comparison.

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>Gas Phase</th>
<th>1-nitrophenanthrene</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
<th>2-nitrophenanthrene</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,3-</td>
<td>1.85 (1.39)</td>
<td>-9.76 (-13.28)</td>
<td>1.87 (1.61)</td>
<td>-9.08(-12.71)</td>
<td>1.91 (1.90)</td>
<td>-8.02(-11.79)</td>
<td></td>
</tr>
<tr>
<td>6,7-</td>
<td>1.05 (1.39)</td>
<td>-13.64(-13.28)</td>
<td>1.23 (1.61)</td>
<td>-13.00(-12.71)</td>
<td>1.49 (1.90)</td>
<td>-12.19(-11.79)</td>
<td></td>
</tr>
<tr>
<td>9,10&lt;sup&gt;b&lt;/sup&gt;-</td>
<td>--------</td>
<td>----------------</td>
<td>--------</td>
<td>----------------</td>
<td>--------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>1,2-</td>
<td>12.89(13.50)</td>
<td>11.82 (12.56)</td>
<td>12.68(13.85)</td>
<td>11.53 (12.99)</td>
<td>12.46 (14.38)</td>
<td>11.19 (13.67)</td>
<td></td>
</tr>
<tr>
<td>2,3-</td>
<td>1.56 (1.39)</td>
<td>-12.88(-13.28)</td>
<td>1.54 (1.61)</td>
<td>-13.04(-12.71)</td>
<td>1.65 (1.90)</td>
<td>-13.11(-11.79)</td>
<td></td>
</tr>
<tr>
<td>3,4-</td>
<td>17.01(14.59)</td>
<td>16.23 (13.12)</td>
<td>17.68(14.89)</td>
<td>17.12 (13.57)</td>
<td>18.64(15.25)</td>
<td>18.44 (14.24)</td>
<td></td>
</tr>
<tr>
<td>6,7-</td>
<td>1.14 (1.39)</td>
<td>-13.65(-13.28)</td>
<td>1.32 (1.61)</td>
<td>-13.1(-12.71)</td>
<td>1.60 (1.90)</td>
<td>-12.26(-11.79)</td>
<td></td>
</tr>
<tr>
<td>9,10&lt;sup&gt;b&lt;/sup&gt;-</td>
<td>--------</td>
<td>----------------</td>
<td>--------</td>
<td>----------------</td>
<td>--------</td>
<td>----------------</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> The PCM(solvent)-B3LYP/6-31+G(d,p)//B3LYP(gas)/6-31G(d) level of theory.

Table 6.4. Free energies of reaction $[\Delta G^{0}_{\text{rxn}}(298K)]$ and free energies of activation $[\Delta G^{\neq}(298K)]$ (kcal/mol) for the isomerization of nitrophenanthrene epoxides to the corresponding oxepines calculated at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level of theory, and comparison with the isomerization of phenanthrene oxides (in parentheses).

Table 6.4 is continued
As shown in Table 6.4, for the isomerization of all of the 2,3-epoxides and 6,7-epoxides derived from any of the nitrophenanthrene regioisomers, all of the free energies of isomerization are less than \(-8.00\) kcal/mol, and free energies of activation are close to

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>Gas Phase $\Delta G^\circ$</th>
<th>$\Delta G^\circ_{\text{trn}}$</th>
<th>Benzene $\Delta G^\circ$</th>
<th>$\Delta G^\circ_{\text{trn}}$</th>
<th>Water $\Delta G^\circ$</th>
<th>$\Delta G^\circ_{\text{trn}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Nitrophenanthrene</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,2-</td>
<td>16.13 (13.50)</td>
<td>15.79 (12.56)</td>
<td>16.88 (13.85)</td>
<td>16.66 (12.99)</td>
<td>18.07 (14.38)</td>
<td>18.03 (13.67)</td>
</tr>
<tr>
<td>2,3-</td>
<td>1.51 (1.39)</td>
<td>-13.21 (-13.28)</td>
<td>1.47 (1.61)</td>
<td>-13.31 (-12.71)</td>
<td>1.51 (1.90)</td>
<td>-13.38 (-11.8)</td>
</tr>
<tr>
<td>6,7-</td>
<td>1.21 (1.39)</td>
<td>-13.32 (-13.28)</td>
<td>1.40 (1.61)</td>
<td>-12.67 (-12.71)</td>
<td>1.71 (1.90)</td>
<td>-11.66 (-11.8)</td>
</tr>
<tr>
<td>4-Nitrophenanthrene</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,2-</td>
<td>12.44 (13.50)</td>
<td>11.11 (12.56)</td>
<td>12.50 (13.85)</td>
<td>11.40 (12.99)</td>
<td>12.54 (14.38)</td>
<td>11.85 (13.67)</td>
</tr>
<tr>
<td>2,3-</td>
<td>-3.21 (1.39)</td>
<td>-16.99 (-13.28)</td>
<td>-3.80 (1.61)</td>
<td>-16.70 (-12.71)</td>
<td>-4.76 (1.90)</td>
<td>-16.24 (-11.79)</td>
</tr>
<tr>
<td>3,4-</td>
<td>17.88 (14.59)</td>
<td>17.61 (13.12)</td>
<td>17.42 (14.89)</td>
<td>16.98 (13.57)</td>
<td>16.58 (15.25)</td>
<td>15.95 (14.24)</td>
</tr>
<tr>
<td>6,7-</td>
<td>0.86 (1.39)</td>
<td>-13.13 (-13.28)</td>
<td>0.92 (1.61)</td>
<td>-12.77 (-12.71)</td>
<td>1.12 (1.90)</td>
<td>-12.17 (-11.79)</td>
</tr>
<tr>
<td>9-Nitrophenanthrene</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,3-</td>
<td>0.94 (1.39)</td>
<td>-13.86 (-13.28)</td>
<td>1.07 (1.61)</td>
<td>-13.31 (-12.71)</td>
<td>1.29 (1.90)</td>
<td>-12.35 (-11.79)</td>
</tr>
<tr>
<td>6,7-</td>
<td>0.93 (1.39)</td>
<td>-12.35 (-13.28)</td>
<td>1.07 (1.61)</td>
<td>-11.82 (-12.71)</td>
<td>1.34 (1.90)</td>
<td>-10.97 (-11.79)</td>
</tr>
<tr>
<td>9,10. b</td>
<td>------------</td>
<td>12.95 (14.38)</td>
<td>11.98 (13.67)</td>
<td>12.12 (11.79)</td>
<td>11.97 (-11.79)</td>
<td>11.76 (13.67)</td>
</tr>
</tbody>
</table>

* a At the PCM(solvent)-B3LYP/6-31+G(d,p)//B3LYP(gas)/6-31G(d) level of theory.
* b Unable to optimize the corresponding oxepines.
zero, regardless of the dielectric constant of the solvent. Therefore, the isomerization of these epoxides to the oxepines should be very facile, and the reactions are exoergic. The exoergicity can be mainly attributed to the increase in aromaticity after the isomerization. An aromatic benzene ring contributes to the aromaticity of the 2,3-epoxides and 6,7-epoxides, but for the corresponding oxepines, an aromatic naphthalene ring can contribute to the aromaticity. Therefore, more favorable aromaticity exists in the oxepines than in the epoxides. The favored valence tautomers are the corresponding oxepines. For the rest of the epoxides listed in Table 6.4, these aromaticity trends are reversed; thus, the rate of the isomerization is much slower and equilibrium favors the epoxide isomers to a significant extent. When the dielectric constant of the solvent increases, the isomerization of the 2,3-, 5,6-, 6,7-, and 7,8-epoxides derived from 1-nitrophenanthrene; the isomerization of the 3,4-, 5,6-, 6,7-, and 7,8-epoxides derived from 2-nitrophenanthrene; the isomerization of the 1,2-, 5,6-, 6,7-, and 7,8-epoxides derived from both 3-nitrophenanthrene and 4-nitrophenanthrene; and the isomerization of the 1,2-, 2,3-, 3,4-, 6,7-, and 7,8-epoxides derived from 9-nitrophenanthrene (shown in Table 6.4 as black) are both thermodynamically and kinetically disfavored since the free energies of reaction and the free energy of activation barriers become greater.

For the isomerization of the 1,2-epoxide derived from 2-nitrophenanthrene and the 3,4-epoxide derived from both 3-nitrophenanthrene and 4-nitrophenanthrene (shown in Table 6.4 as red), the solvent effect is reversed: when the dielectric constant of the solvent increases, both free energies of reaction and free energies of activation become smaller, and the isomerization is more facile and more feasible. For the rest of the epoxides (shown in Table 6.4 as blue), the solvent effect does not give trends on the
isomerization. Compared with the corresponding oxide without the nitro group, the isomerization of the 1,2-, 3,4-, 5,6-, 6,7-, and 7,8-epoxides derived from 1-nitrophenanthrene; the isomerization of the 1,2-, 5,6-, 6,7-, and 7,8-epoxides derived from 2-nitrophenanthrene; the isomerization of the 3,4-, 5,6-, and 7,8-epoxides derived from 3-nitrophenanthrene; the isomerization of the 1,2-, 2,3-, 5,6-, and 7,8-epoxides derived from 4-nitrophenanthrene; and the isomerization of the 1,2-, 2,3-, 3,4-, 5,6-, and 7,8-epoxides derived from 9-nitrophenanthrene are both thermodynamically and kinetically more favored regardless of the solvent effects since both the free energies of reaction and the free energy of activation barriers are smaller in the gas phase, in benzene and in water, than that for the oxides without nitro groups; thus, the nitro group facilitates the isomerization. For the isomerization of 1-nitrophenanthrene-2,3-epoxide, the isomerization of 2-nitrophenanthrene-3,4-epoxide, the isomerization of 3-nitrophenanthrene-1,2-epoxide and the isomerization of 4-nitrophenanthrene-3,4-epoxide, the existence of the nitro group disfavored the isomerization both thermodynamically and kinetically. The isomerization of 9-nitrophenanthrene-6,7-epoxide, when compared with the oxide without the nitro group, is more favored kinetically, but less favored thermodynamically. For the isomerization of the remaining epoxides, the existence of the nitro group gives complicated effects when the solvent is concerned since no trends can be seen when the dielectric constant increases.

6.3.5 Nitropyrene

Nitropyrene exists in three regioisomeric forms: 1-nitropyrene, 2-nitropyrene and 4-nitropyrene. The possible epoxides are: 1,2-, 2,3-, 4,5-, 6,7-, 7,8- and 9,10-epoxides
derived from 1-nitropyrene; 1,2-, 4,5- and 6,7-epoxides derived from 2-nitropyrene; and 1,2-, 2,3-, 4,5-, 6,7-, 7,8- and 9,10-epoxides derived from 4-nitropyrene. For the isomerization of the 4,5- and 9,10-epoxides derived from 1-nitropyrene and 4-nitropyrene, and the isomerization of the 4,5-epoxide derived from 2-nitropyrene, the aromaticity from the aromatic phenanthrene ring disappears after isomerization and the energies of the corresponding oxepines are too high to be optimized successfully. The calculated free energies of reaction and the free energies of activation in the gas phase, benzene, and water for the isomerization of the other epoxides are listed in Table 6.5.
Table 6.5. Free energies of reaction [$\Delta G^0_{\text{rxn}}(298K)$] and free energies of activation [$\Delta G^\neq(298K)$] (kcal/mol) for the isomerization of nitropyrene epoxides to the corresponding oxepines calculated at the B3LYP/6-31+G(d,p)//B3LYP(gas)/6-31G(d) level of theory, and comparison with the isomerization of the parent pyrene oxides (in parentheses).

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>Gas phase</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta G^\neq$</td>
<td>$\Delta G^0_{\text{rxn}}$</td>
<td>$\Delta G^\neq$</td>
</tr>
<tr>
<td>1,2-</td>
<td>8.82 (9.66)</td>
<td>3.14 (3.20)</td>
<td>8.51 (9.98)</td>
</tr>
<tr>
<td>2,3-</td>
<td>11.52 (9.66)</td>
<td>8.11 (3.20)</td>
<td>12.38 (9.98)</td>
</tr>
<tr>
<td>4,5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6,7-</td>
<td>8.90 (9.66)</td>
<td>2.39 (3.20)</td>
<td>9.02 (9.98)</td>
</tr>
<tr>
<td>7,8-</td>
<td>9.23 (9.66)</td>
<td>3.11 (3.20)</td>
<td>9.45 (9.98)</td>
</tr>
<tr>
<td>9,10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**1-nitropyrene**

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>Gas phase</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta G^\neq$</td>
<td>$\Delta G^0_{\text{rxn}}$</td>
<td>$\Delta G^\neq$</td>
</tr>
<tr>
<td>1,2-</td>
<td>9.45 (9.66)</td>
<td>3.47 (3.20)</td>
<td>9.36 (9.98)</td>
</tr>
<tr>
<td>4,5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6,7-</td>
<td>9.21 (9.66)</td>
<td>2.83 (3.20)</td>
<td>9.44 (9.98)</td>
</tr>
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</table>

**2-nitropyrene**

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>Gas phase</th>
<th>Benzene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Water&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>$\Delta G^\neq$</td>
<td>$\Delta G^0_{\text{rxn}}$</td>
<td>$\Delta G^\neq$</td>
</tr>
<tr>
<td>1,2-</td>
<td>9.06 (9.66)</td>
<td>4.23 (3.20)</td>
<td>9.50 (9.98)</td>
</tr>
<tr>
<td>2,3-</td>
<td>8.38 (9.66)</td>
<td>2.86 (3.20)</td>
<td>8.55 (9.98)</td>
</tr>
<tr>
<td>4,5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6,7-</td>
<td>9.33 (9.66)</td>
<td>2.86 (3.20)</td>
<td>9.53 (9.98)</td>
</tr>
<tr>
<td>7,8-</td>
<td>9.11 (9.66)</td>
<td>2.41 (3.20)</td>
<td>9.26 (9.98)</td>
</tr>
<tr>
<td>9,10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**4-nitropyrene**

<sup>a</sup> At the PCM(solvent)-B3LYP/6-31+G(d,p)//B3LYP(gas)/6-31G(d) level of theory.

<sup>b</sup> Unable to optimize the corresponding oxepines.
As shown in Table 6.5, none of the quantities are negative, and all of the quantities are less than 14 kcal/mol. Therefore, at room temperature, barrier heights are small but the reactions are all endoergic: the epoxides remain the main component to a significant extent at equilibrium, even while isomerization is feasible in all cases. The isomerization of 1-nitropyrene-2,3-epoxide is the least favored, both thermodynamically and kinetically, since both the free energy of reaction and the free energy of activation for isomerization are the largest. When the dielectric constant of the solvent increases, both $\Delta G_{\text{rxn}}^0$ and $\Delta G^\ddagger$ for the isomerization of the 2,3-, 6,7- and 7,8-epoxides derived from 1-nitropyrene; the 6,7-epoxide derived from 2-nitropyrene; and the 1,2-, 2,3-, 6,7-, and 7,8-epoxides derived from 4-nitropyrene are increased. Consequently, the isomerizations of these epoxides are disfavored both thermodynamically and kinetically in the solvent with a higher dielectric constant. On the other hand, for 1-nitropyrene-1,2-oxide and 2-nitropyrene-1,2-oxide, when the dielectric constant of the solvent increases, the isomerization is more favored thermodynamically and kinetically. Compared with the isomerization of the oxide without nitro group, the isomerization of the 1,2- and 6,7-epoxides derived from 1-nitropyrene and 2-nitropyrene along with the 2,3-, 6,7- and 7,8-epoxides derived from 4-nitropyrene are both thermodynamically and kinetically more favored. But for the 2,3- and 7,8-epoxides derived from 1-nitropyrene, the isomerization is less favored than the isomerization of the oxides without the nitro group. For the isomerization of 4-nitropyrene-1,2-epoxide, the existence of the nitro group accelerates the isomerization rate but reduces the equilibrium constant of the isomerization (hence in favor of the epoxide) in that the free energy of reaction is more endoergic and the free
energy of activation is smaller than that for the isomerization of the arene oxide without the nitro group.

This aspect may be a significant effect with regard to the mutagenicity and toxicity of such large NPAHs. If substituent effects, such as nitro groups, can favor the equilibrium towards the epoxide, then subsequent reaction with epoxide hydrase may be more favorable, thus leading to enhanced formation of such diol-epoxide electrophiles for subsequent reactions with nucleophilic DNA.

Another important application of our calculations involves predictions of the absolute configurational stability of optically active nitrated arene oxides and of the relative stability of the epoxide and oxepine isomers. When the free energy of activation barriers, \( \Delta G^\neq(298\text{K}) \), is small, the isomerization occurs very easily, and the optically active nitrated arene epoxide is easily racemized. When the isomerization free energy \( \Delta G^0_{\text{rxn}}(298\text{K}) \) is negative, the oxepine is more stable than the epoxide, at equilibrium. The more positive the \( \Delta G^\neq(298\text{K}) \), the more stable the absolute configuration of the epoxide; the more positive the \( \Delta G^0_{\text{rxn}}(298\text{K}) \), the more stable the epoxide, and the less stable the oxepine. For example, the racemizations of the optically active 2,3- and 6,7-epoxides derived from both 1-nitronaphthalene and 2-nitronaphthalene occur readily, and the corresponding oxepines are the favored isomers, while the racemization of optically active 1-nitrophenanthrene-5,6-oxide occurs very slowly, and the epoxide is the primary isomer at equilibrium.
6.4 Conclusions

In this work, we explored the isomerization of NPAH oxides, derived from nitrobenzene, nitronaphthalene, nitroanthracene, nitrophenanthrene and nitropyrene, to the corresponding oxepines, using density functional theory calculations. The calculations quantitatively demonstrate the favorableness of the isomerization at room temperature on energetic grounds, both thermodynamically and kinetically. The aromaticity plays an important role on the isomerization process: if the aromaticity increases during the isomerization, the isomerization is facile, and the forward reaction (to form the oxepine) is favored. Conversely, if the aromaticity decreases, the isomerization is slower and the epoxide is the primary valence isomer at equilibrium. The results elucidate the origin of the racemization of the optically active arene oxides. The solvent effects on the isomerization of NPAH oxides are different from solvent effects on the isomerization of PAHs. The dielectric constant of the solvent plays a different role for different epoxides: for some epoxides, a solvent with a high dielectric constant can favor the isomerization, both thermodynamically and kinetically; for some epoxides, solvation effects are reversed; for some epoxides, a solvent with a high dielectric constant can accelerate the isomerization and accompanying reduce the equilibrium constant of the isomerization, or decelerate the isomerization and increase the equilibrium constant. The effect of the nitro group on the isomerization is dependent on the location of the oxirane and the structure of the NPAH. For large NPAH systems, the epoxide is favored at equilibrium and this aspect may be significantly relevant to the mutagenicity and toxicity of substituted PAHs.
6.5 References


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