

Reactions of phloroglucinols with radical species, a theoretical study in different media

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DECLARATION

I, Kgalaletso Precious Otukile, hereby declare that this dissertation is a presentation of my original research work for the degree MSc in Chemistry, and has not been submitted to this institution or any other South African institution of higher learning. Every contribution of others involved in this dissertation has been acknowledged. All sources used have been referenced. The work was done under the supervision of Prof. M. M. Kabanda of the Chemistry Department at the North-West University, South Africa.

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ABSTRACT

A theoretical study on the reactions of phloroglucinol (FG) and phloroacetophenone (THAP) with $\bullet\text{OH}$ and $\bullet\text{OOH}$ has been performed through hydrogen atom transfer (HAT), single electron transfer-proton transfer (SET-PT), sequential proton-loss electron-transfer (SPLET) and the oxidation mechanisms. The aim of the investigation has been to determine the preferred reaction mechanism relating to the radical scavenging activity of the compounds. The objectives of the study have been to determine the reaction enthalpies for the HAT, SET-PT and SPLET mechanisms, geometric, electronic, energetic and kinetic properties for the HAT and oxidation mechanisms. The DFT/M06–2X, DFT/BHLYP and DFT/MPW1K methods have been utilised in conjunction with either the standard 6-31++G(d,p) basis set or the extended 6-311++G(3df,2p) basis set. The selected DFT functionals have been benchmarked using the CBS-QB3 compound method for their ability to estimate barrier heights. The study has been performed *in vacuo*, in benzene and in ethanol media. Analysis of the reaction enthalpies suggests that the preferred mechanism is the HAT mechanism; reactions involving the studied compounds with $\bullet\text{OH}$ are exothermic in nature while reactions involving $\bullet\text{OOH}$ are slightly endothermic in nature. THAP has a higher radical scavenging ability than FG; this result is in agreement with the experimental findings. The preferred reactive site of THAP for the abstraction of the free phenolic H atom is the *ortho* position. The direct hydrogen abstraction mechanism provides the smallest branching ratio with respect to $\bullet\text{OH}$ addition mechanism, indicating that hydrogen atom transfer mechanism occurs largely through the addition mechanism. More importantly, the phenoxyl radical, forming through the addition-elimination mechanism, prefers to form under basic conditions. The oxidation mechanism, resulting in tetrahydroxybenzene for reactions involving FG and THAP with $\bullet\text{OH}$, prefers to occur under neutral conditions in the presence O_2 . The reactions involving phloroglucinols and $\bullet\text{OOH}$ largely occur through direct hydrogen abstraction mechanism, forming a phenoxyl radical and hydrogen peroxide. The spin density and branching ratio values indicate that the most reactive site for the THAP + $\bullet\text{OOH}$ reaction is the *ortho* position with respect to the substituted acyl chain. Reactions performed in polar medium are more kinetically preferred than those performed *in vacuo* and in non-polar media. The DFT/M06–2X method provides barrier heights which are closer to the barrier heights determined using the CBS-QB3 method.

Keywords: Phloroglucinols, Radical scavenging, Solvent effect, Intermolecular hydrogen bonds

PUBLICATIONS AND CONFERENCE PRESENTATIONS

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1. **K. P. Otukile**, M. M. Kabanda, A DFT mechanistic, thermodynamic and kinetic study on the reaction of 1, 3, 5-trihydroxybenzene and 2, 4, 6-trihydroxyacetophenone with $\bullet\text{OOH}$ in different media, J. Theor Comput Chem, 18 (**2019**)1950023 (28 pages).
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LIST OF ABBREVIATIONS

ACFG	Acylated phloroglucinol
A-E	Addition-elimination
AIM	Atoms in molecules
AMBER	Assisted model building with energy refinement
ASC	Apparent surface charge
B3LYP	Becke's three-parameter-Lee Yang Parr
B88	Becke's 1998
B95	Becke's 1995
B96	Becke's 1996
BCP	Bond critical point
BDE	Bond dissociation enthalpy
BFGS	Broyden-Fletcher-Goldfarb-Shanno
BHHLYP	Becke half-half Lee Yang Parr
CBS	Complete basis set
CCSD(T)	Coupled cluster single double and triple
CHARMM	Chemistry at Harvard macromolecular mechanics
COSMO	Conductor-like screening model
DFT	Density functional theory
DHAA	Direct hydrogen atom abstraction
ETE	Electron transfer enthalpy
GGA	Generalised gradient approximation
HAT	Hydrogen atom transfer
H-bond	Hydrogen bond
HF	Hartree Fock
ICM	Image charge method
IEF-PCM	Integral equation formalisation polarisable continuum
IP	Ionisation potential
IRC	Intrinsic reaction coordinate
LDA	Local density approximation
LST	Linear synchronous transit
LYP	Lee Yang Parr

M06–2X	Minnesota meta hybrid with double the amount of nonlocal exchange
MBJ	Modified Becke-Johnson
MEP	Minimum energy path
MM	Molecular mechanics
MP	Møller Plesset
MP2	Second order Møller Plesset
MPW1K	Modified Perdew-Wang 1-parameter for kinetics
PA	Proton affinity
PBE	Perdew-Burke-Enzerhof
PCM	Polarizable continuum model
PDE	Proton dissociation enthalpy
PES	Potential-energy surface
FG	Phloroglucinol
THAP	Phloroacetophenone
QM	Quantum mechanics
QM/MM	Quantum mechanics and molecular mechanics
QST	Quadratic synchronous transit
QTAIM	Quantum theory of atoms in molecules
RCP	Ring critical point
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SAS	Solvent accessible surface
SES	Solvent-excluded surface
SET	Single electron transfer
SET-PT	Single electron transfer-proton transfer
SMD	Solvation model density
SPLET	Sequential proton-loss electron-transfer
SR1	Symmetric rank one
STQN	Synchronous transit-guided quasi-Newton
TPSS	Tao, Perdew, Staroverov and Scuseria
TST	Transition state theory

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CHAPTER 1

INTRODUCTION

1.1 Significance of the study

Phloroglucinol (1, 3, 5-trihydroxybenzene) is a phenolic compound consisting of a benzene ring that is substituted with three hydroxyl (OH) groups at *meta* position with respect to each other. An acylated phloroglucinol is a phloroglucinol derivative substituted with an acyl group, which contains a double bonded oxygen atom and an alkyl group. The schematic representation of a phloroglucinol (FG) moiety and an acylated phloroglucinol (ACFG) molecule are shown in Figure 1.1. Phloroglucinols (both acylated and non-acylated derivatives) are largely found in plants (i.e., algae [1–3]), fungal [4–7] and bacterial [8, 9] species. They exhibit various biologically related activities, including antioxidant, antifungal, antimalarial and antitumor [10–17]. The antioxidant property of phloroglucinols allows them to be considered for possible utilisation in the production of medications, cosmetics and food additives; in the pharmaceutical industry, phloroglucinols are utilised to manufacture of medicinal drugs (e.g., for the purpose of treating degenerative diseases such as neurological disorder, cancer, malaria and cardiovascular diseases [16–20]); phloroglucinols may be utilised in the cosmetic industry to manufacture formulas for treatment of skin related diseases as well as for cosmetic purposes [20–24], and in the food additive industry, the antioxidant activity of phloroglucinols is utilised to provide the long-shelf life to various food products [25].

Degenerative diseases may arise as a result of oxidative stress, which is defined as an imbalance between the body's defence mechanism and the excess free radical species within the biological system [1, 26–29]. When the body's defence mechanism (i.e., the immune system) is weak, it may be unable to regulate the excess free radicals; as a consequence, the excess free radicals may cause lipid peroxidation, which in turn may

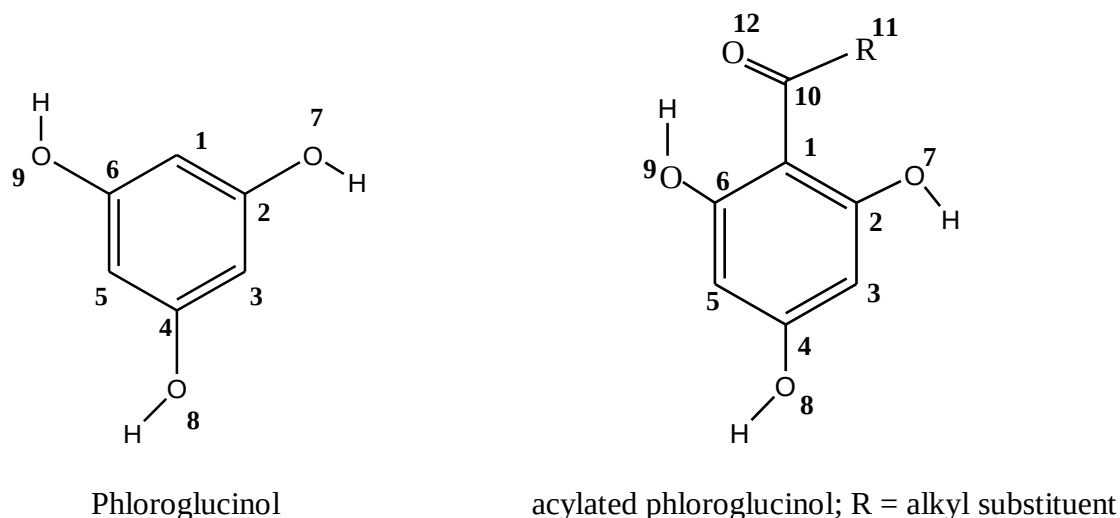


Figure 1.1: Schematic representation of phloroglucinol (FG) and acylated phloroglucinol (ACFG). The numbering on each atom represent the numbering format that is chosen for utilisation throughout the study for the purpose of describing the features of the compounds.

damage biological macromolecules (e.g., proteins and nucleic acids [1, 19, 26]) within the biological system. In this way, the body's defence mechanism needs to be supplemented with antioxidant molecules, such as phloroglucinols with the purpose of regulating the excess free radicals in the biological system. Free radical species are defined as atoms or molecules with an unpaired electron; because of their unpaired electrons, they are usually unstable and highly reactive. Free radicals may exist as neutral, anionic and cationic molecular species. Radical species found within the biological system (that may cause oxidative stress when in excess) include; reactive oxygen species (ROS), such as hydroxyl radical ($\cdot\text{OH}$) and superoxide anion radical [1, 19, 26–29], and reactive nitrogen species (RNS), such as nitric oxide radical and nitrogen dioxide radicals [30–34]). The negative impact of ROS and RNS in the biological system, when they are in excess, requires that they be eradicated from the biological system by supplementing the body's defence mechanism with supplement antioxidant molecules.

The supplement antioxidant molecules are divided into two groups; those that are synthetic in nature and those that are natural in nature [35, 36]. Synthetic antioxidants,

although highly popular, tend to cause a number of side effects within the biological system, including suppressing the immune system, disrupting the production of natural antioxidants in the body and disrupting biochemical pathways in the biological system [37]. As a result, there is an increasing trend towards utilisation of naturally obtained antioxidant (e.g., those that are obtained from plant sources). Phloroglucinol derivatives are examples of compounds derived from plant sources and which possess antioxidant properties. It is for this reason that they are preferably considered as possible candidates for utilisation in the design of supplementary antioxidant drugs. Therefore, the reaction of some radical species, found within the biological system, with selected phloroglucinols is an important subject to undertake in order to provide an understanding on the reaction mechanisms that would be involved within the biological system.

Although FG and its derivatives may be utilised to eradicate excess ROS and RNS in the biological system, the action is reversed when considering their presence in the atmospheric environment, where they are considered as pollutants and radicals such as $\bullet\text{OH}$ are considered as reagents that can aid their eradication. $\bullet\text{OH}$ is also found extensively within the atmosphere where it is known to undergo atmospheric reactions with organic substrates [38–41]. It plays an important role in the oxidative processes in the atmosphere, leading to the degradation of atmospheric pollutants, such as phenolic compounds [38]. FGs may be found in the atmosphere; their existence in the atmosphere may be attributed to various processes, such as cloud seeding [42–44]. For this reason, their elimination from the atmosphere through reaction with $\bullet\text{OH}$, present in the atmosphere, can be envisaged.

The aim of the work presented in this dissertation has been to investigate the radical scavenging mechanisms of phloroglucinols. Two phloroglucinols have been selected for the study, which are the parent phloroglucinol compound and phloroacetophenone (THAP), which is the unit compound for ACFG. The two radical species that have been selected for reaction with phloroglucinols are the hydroxyl radical ($\bullet\text{OH}$) and the hydroperoxyl radical ($\bullet\text{OOH}$) species; these radicals are found to be highly reactive within the biological system and $\bullet\text{OH}$ is found to be reactive also in the atmosphere.

The objective of the study include performing quantum mechanical investigations on the reactions involving FG and THAP molecules with $\bullet\text{OH}$ and $\bullet\text{OOH}$ in order to determine

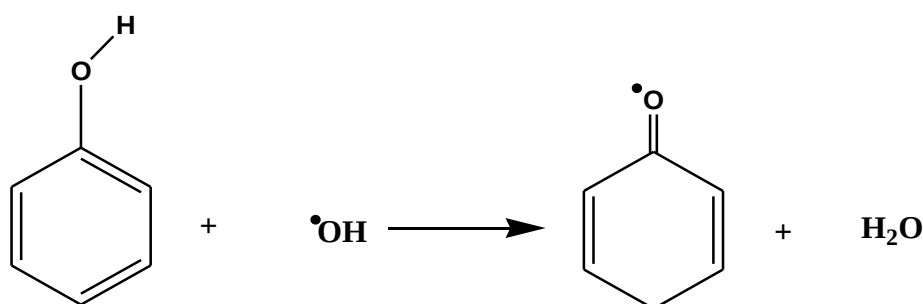
- the reaction enthalpies (i.e., bond dissociation enthalpy, proton affinity, proton dissociation enthalpy, ionization potential energy and electron transfer enthalpy) related to various reaction mechanisms,
- the geometric properties such as bond length, bond angle and torsion angle of the isolated and reaction species involved in the different reaction mechanisms,
- the electronic properties (e.g., electron density) of the various reaction species, in order to elucidate the type of bonding involved within the reaction species,
- the distribution of the electron spin density on the product species,
- the most preferred reaction mechanisms, which can be identified by analysis of some of the thermodynamic and kinetic features for the various reactions,
- the effect of the solvent on the geometric, energetic and kinetic parameters of the species involved in the reactions.

The study is performed in gaseous phase (i.e., *in vacuo*) in order to mimic the situation in the atmosphere (e.g., in the presence of smog), where phloroglucinol derivatives constitute part of pollutants that might react with radical species such as $\bullet\text{OH}$. The study is also performed in the presence of two solvents; benzene and ethanol. The selection of these two solvents is meant to simulate the environment within biological systems, where both non-polar and polar media exists. Antioxidants, including FG and THAP, may be found to exhibit their activities within the lipid membrane regions of the biological system in order to, for instance, inhibit lipid peroxidation. For this reason, a solvent that can mimic the lipid membrane region is needed in order to understand the reactivity of FG and THAP towards $\bullet\text{OH}$ and $\bullet\text{OOH}$. The benzene medium is chosen for utilisation in this study for the purpose of representation of the lipid membrane part of the biological systems; it has been utilised extensively in the study of antioxidants to model the polarity of the lipid membrane part of biological systems [45, 46]. Ethanol solvent, which is a polar solvent in nature, has also been utilised extensively in experimental studies of antioxidant molecules, largely because, although it is not found within biological systems as a solvent, it is considered safe for human consumption [47, 48]; its polar protic nature makes it a suitable solvent for assisting the reactivity of phenol and its derivatives towards

free radical species [49]. Water solvent, although would be the most appropriate solvent to model the reactions in order to compare with biological conditions, it is not an experimentally preferred solvent in the study of antioxidant mechanisms, for this reason there are no experimental results obtained in the water medium (e.g., rate constant values) by which one can compare with the theoretically obtained data in relation to reactivity of phenols with radical species. It is for this reason that the ethanol solvent medium is preferred to the water solvent for the current study.

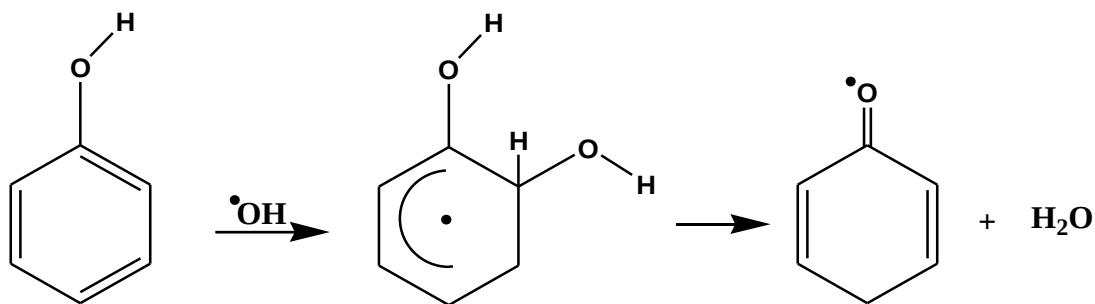
1.2 Reactions of phenols with radical species

There have been significant experimental and theoretical data from studies related to reactions between phenol (and its derivatives) and free radical species [30–33, 50–64]; the results of the study on such models provide information on the mode in which the reaction between polyphenolic compounds and radical species, such as $\bullet\text{OH}$, may occur. There are three main mechanistic pathways by which phenol reacts with $\bullet\text{OH}$ [50–66]; the first pathway (Scheme 1) is the direct hydrogen atom abstraction (DHAA) mechanism. This pathway results in the production of the phenoxyl radical species [57, 58, 65, 66];



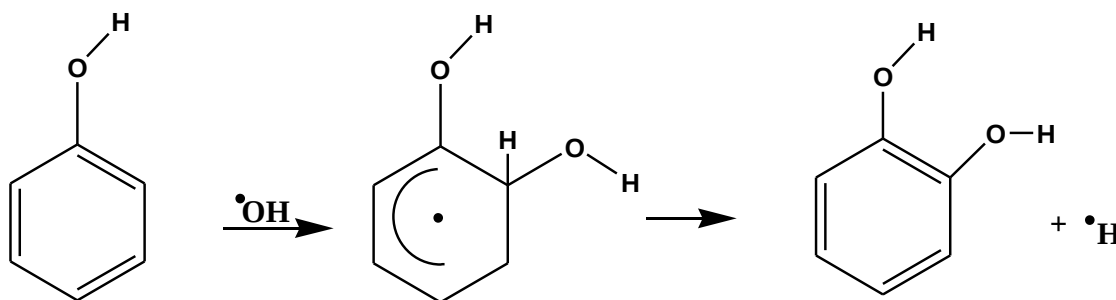
Scheme 1: Schematic representation of the DHAA mechanism for phenol + $\bullet\text{OH}$ resulting in the formation of phenoxyl radical and water byproduct.

the second pathway (Scheme 2) also results in the production of the phenoxyl radical but passes through the addition of $\bullet\text{OH}$ on the ring. Once the sp^3 carbon-centred intermediate is formed, it is followed by elimination of a water molecule [50–58, 65, 66]. The overall mechanism is known as addition-elimination (A-E) mechanism.



Scheme 2: Schematic representation for the A-E mechanism of phenol + $\bullet\text{OH}$ leading to the formation of a stable phenoxyl radical and a water molecule.

The third pathway (Scheme 3) is the oxidation of phenol resulting in the formation of high order polyphenol product. It is a reaction in which $\bullet\text{OH}$ adds first on the ring, giving rise to a dihydroxycyclohexadienyl radical intermediate. The intermediate species reacts with other reactive neutral species within the environment to eliminate the H radical in order to form polyphenol product.



Scheme 3: Schematic representation for the oxidation mechanism of phenol + $\bullet\text{OH}$, resulting in the formation of a high-order polyphenolic (catechol) compound.

The addition of $\bullet\text{OH}$ (for the oxidation mechanism) is not restricted to only the *ortho* position but may also involve the *meta* and the *para* positions on the original phenol derivative. For instance, a reaction of phenol with $\bullet\text{OH}$ may result in the formation of 1,2-dihydroxybenzene (scheme 3) as well as 1,4-dihydroxybenzene [57, 65, 66]. The elimination of $\bullet\text{H}$ from the intermediate species obtained in Scheme 3 may be facilitated by addition of other species into the reaction at the intermediate stage; for instance, the oxygen molecule has been added in the reaction of phloroglucinol with $\bullet\text{OH}$, resulting in the formation of the hydroperoxyl radical byproduct [57];



Since phloroglucinol is a phenol derivative; it would be meaningful to anticipate that in the study of $\text{FG} + \bullet\text{OH}$ reaction, the possibility of the formation of 1, 2, 3, 5-tetrahydroxybenzene product be investigated. However, information from phenol + $\bullet\text{OH}$ may not provide direct application to understand the reaction mechanism involving derivatives such as FG, since different systems may have different structural properties (e.g., in the case of FG all *meta* position of the benzene ring are substituted with phenolic OH groups). Therefore, it is imperative that the phloroglucinol derivatives be treated/studied separately from phenol derivatives since the structural features of phloroglucinol derivatives is significantly different from that of isolated phenol; the difference in the structural features may impact strongly on the results of such studies (e.g., in terms of the preferred reaction mechanism and reaction rate). Moreover, the high number of hydroxyl groups on the phloroglucinol moiety in comparison with phenol

moiety suggests the possibility that phloroglucinol derivatives may have higher antioxidant properties than phenol derivatives. This makes the study presented in this dissertation worth of investigation. The results of the investigation on FG + $\bullet$ OH may then be compared with the numerous data already available on phenol + $\bullet$ OH in order to identify the similarities and differences between the two phenolic systems.

Experimental findings on FG + $\bullet$ OH have shown that the rate of the water elimination from the intermediate species (in A-E mechanism) under neutral conditions is not kinetically favoured unless the reaction is performed with the inclusion of a catalyst [50, 54]. In the case of oxidation mechanism, FG + $\bullet$ OH may result in the formation of 1,2,3,5-tetrahydroxybenzene [50]. The results of the study presented in this dissertation provide the first theoretical investigation on the reactivity of FG towards $\bullet$ OH, considering the A-E mechanism; the investigation is reported in the absence and the presence of a base catalyst in order to compare trends in the two cases. The theoretical results on the oxidation mechanism in the absence and presence of O₂ are also presented for the first time. The results obtained in this study are compared with the previous experimental and theoretical data on the reaction of phenol with $\bullet$ OH as well as experimental findings on the reaction of FG and $\bullet$ OH.

The ability of FG and THAP to inhibit lipid peroxidation, by scavenging radical species such as $\bullet$ OOH, have been reported from experimental findings [65–70]. The findings suggest that THAP has greater tendency to inhibit lipid peroxidation than FG, which implies that phloroglucinol derivatives that contain the acyl group could be considered more effective antioxidants than compounds that contain only the FG moiety. Despite the fact that experimental and theoretical studies on the antioxidant activities and properties of THAP and FG have been reported, there is still more information that can be investigated concerning the reactivity of these compounds with biologically related radical species. For instance, there has not been a thorough investigation of the reaction mechanism involving either FG or THAP with $\bullet$ OOH to elucidate the thermodynamic and kinetic features associated with the antioxidant mechanisms of these compounds. Moreover, although the theoretical studies on the antioxidant properties of THAP and FG have largely been on the hydrogen atom transfer and single electron transfer mechanisms

[46, 69, 70], the antioxidant mechanism is also better studied by taking into account the sequential proton-loss electron-transfer mechanism. In other words, it is important that all the possible mechanisms (i.e., hydrogen atom transfer, single electron transfer-proton transfer and sequential proton-loss electron-transfer) are investigated before determining those that are largely preferred for the overall reaction.

Despite the fact that the hydrogen atom transfer mechanism related to the reactions of phenols with $\bullet\text{OH}$ can occur through either the DHAA mechanism or A-E mechanism, previous studies on the reactions of phenol derivatives with $\bullet\text{OOH}$ have shown that the HAT mechanism largely proceeds through the DHAA mechanism [71, 72]. For this reason, the investigation on the reaction of FG and THAP with $\bullet\text{OOH}$ considered only the DHAA mechanism.

1.3 Overview of the dissertation

The work presented in this dissertation is organised in such a manner that first the theoretical background to the study is presented in Chapter 2. This chapter covers information related to theoretical background on the methodology as well as on the approach for studying reaction mechanisms. Chapter 3 provides details on the selected methods for the study; it introduces the computational procedures utilised as well as the computational programs selected for utilisation in the study reported in this dissertation. Chapter 4 and chapter 5 present the results of the findings and their corresponding discussions; chapter 4 reports the results and discussion on the study of the reactions of selected phloroglucinols with $\bullet\text{OH}$ while Chapter 5 provides information on the results and discussion for the reactions of selected phloroglucinols with $\bullet\text{OOH}$. Chapter 6 provides conclusions and recommendations for future work; it provides an overall picture of the study in a comparative manner between the findings reported in chapter 4 and chapter 5.

CHAPTER 2

THEORETICAL BACKGROUND

2.1 Density functional theory

Density functional theory (DFT) is one of the electronic structure methods used to determine the molecular properties (e.g., molecular energy, dipole moment and magnetic properties) for a ground state of a molecular system. The molecular properties are obtained by solving the Schrödinger equation using the electron probability density (ρ) parameter rather than the wavefunction (Ψ), which is used in other electronic structure methods, such as the Hartree-Fock (HF), Møller–Plesset (MP) and complete basis set (CBS) methods [73–80]. CBS methods are composite methods not to be confused by the uninitiated methods, such as HF and MP methods; they are schemes used to extrapolate results obtained with a given uninitiated method and different basis sets to the complete basis set limit. DFT provides a better estimation of the properties of molecular systems than HF because DFT takes into consideration the electron correlation effects, which are largely neglected in HF calculations [80–86]. Although both MP and CBS methods can be considered to be more accurate than DFT, they are computationally more expensive than DFT, making them less valuable for utilisation when studying middle-size molecules (e.g., molecule with 20 or more atoms) to large size molecules (e.g., molecule with 80 or more atoms). Moreover, DFT based methods are increasingly providing results that are closer to experimental findings on properties related to thermochemistry and reaction kinetics [87–89] than second order Møller–Plesset (MP2) method. In fact, a significant number of findings have shown that second order Møller–Plesset (MP2) method tends to overestimate the barrier heights for chemical reactions; some DFT methods, however, tends to provide barrier heights that are close to experimental findings [90, 91]. DFT methods may also provide results that are close to results obtained using some highly expensive theoretical methods such as Coupled cluster (CC) method with a

full treatment of single, double and triple excitations. Therefore, DFT methods are increasingly finding application in the study of many molecular properties associated with thermochemistry and reaction kinetics, to elucidate the nature of such reaction mechanisms, in place of more expensive MP2, CBS and CCSD(T), which are all based on wavefunction approach. Since the current work is concerned with the investigation of reaction mechanisms of phloroglucinol derivatives with selected radical species, it is meaningful that the DFT method is selected for the study with the aim of obtaining results within the limited time of the study. Moreover, with the selection of the DFT method as a first choice method for the study conducted in this dissertation, it is imperative that a theoretical background covering the mathematical foundation of the DFT methods towards obtaining molecular properties (such as the energy of a system) be detailed. What follows is therefore an attempt to provide a theoretical framework for the development of DFT in determining molecular properties of systems.

2.1.1 Hamiltonian expression in terms of the electron density

Consider the Schrodinger equation for a system associated with the electronic molecular Hamiltonian (H) in terms of the wavefunction;

$$H\Psi = E\Psi, \quad (2.1)$$

where E is the total energy of the system, Ψ is the n -electron wavefunction; that depends on the identities and positions of nuclei and on the total number of electrons, H is a Hamiltonian operator; which consists of the kinetic energy terms and the potential energy terms of both electrons and nuclei constituting the molecular system. To obtain the Kohn-Sham equations similar to the wavefunction type of an equation, we consider the ground state electronic energy given as a function of electron density ρ :

$$E[\rho] = T[\rho] + \int \rho(\mathbf{r}) V(\mathbf{r}) d\mathbf{r} + E_{ee}[\rho], \quad (2.2)$$

where the first term ($T[\rho]$) is the electronic kinetic energy, the second term ($\int \rho(\mathbf{r}) V(\mathbf{r}) d\mathbf{r}$) is the external potential due to electron-nucleus interaction and the last term ($E_{ee}[\rho]$) is

the electron-electron interaction energy. The electron density is itself a function of position $\mathbf{r}$. The relationship between a one-electron spatial orbitals ψ_i ($i= 1, 2, \dots, n$) and the electron density is expressed through the equation

$$\rho(\mathbf{r}) = \sum_{i=1}^n |\psi_i(\mathbf{r})|^2, \quad (2.3)$$

where n is the number of electrons; it has an expression of the form;

$$n(\mathbf{r}) = \int \rho(\mathbf{r}) d\mathbf{r}. \quad (2.4)$$

The kinetic energy expression in equation 2.2 has the form;

$$T[\rho] = -\frac{\hbar^2}{2m_e} \sum_{i=1}^n \int \psi_i^*(\mathbf{r}) \nabla^2 \psi_i(\mathbf{r}) d\mathbf{r}. \quad (2.5)$$

The nuclear attraction potential energy term $v(\mathbf{r})$ in equation 2.2 is an external attraction Coulomb potential; it has the form;

$$v(\mathbf{r}) = -\sum_{\alpha} \frac{Z_{\alpha}}{r_{i\alpha}} \text{ in atomic units,} \quad (2.6)$$

where Z_{α} is the atomic charges for nuclei and $r_{i\alpha}$ is the separation between the nucleus and electron distances.

The last term in equation 2.2 is given by the expression;

$$E_{ee}[\rho(\mathbf{r})] = \frac{1}{2} \int \frac{\rho(\mathbf{r}_1)\rho(\mathbf{r}_2)}{|\mathbf{r}_1 - \mathbf{r}_2|} d\mathbf{r}_1 d\mathbf{r}_2 + E_{xc}[\rho(\mathbf{r})], \quad (2.7)$$

where the first term in the equation is the electron-electron interaction and the second term ($E_{xc}[\rho(\mathbf{r})]$) is the non-classical exchange-correlation energy arising from the exchange and correlation non-classical interactions. The exchange interactions are usually associated with parallel spin density (i.e., the two electrons have the same spin) and it arises from the antisymmetry properties of fermion wavefunctions. Correlation interactions arise from the fact that there exist instantaneous Coulomb repulsive forces between electrons.

If the wavefunctions are required to fulfil the orthogonal and the normalisation conditions then;

$$\int \psi_i^*(\mathbf{r}) \psi_j(\mathbf{r}) d\mathbf{r} = \delta_{ij}. \quad (2.8)$$

Consider equation 2.2 and write the sum of the first term and the last term as $F[\rho]$;

$$F[\rho] = T[\rho] + E_{ee}[\rho]. \quad (2.9)$$

Consider the variation principle for the density of states, which states that ground-state energy for a given $V(\mathbf{r})$ is obtained by minimising $E[\rho]$ with respect to ρ for fixed $V(\mathbf{r})$, and the ρ that yields the minimum is the density in the ground state. Minimising $E[\rho]$ with respect to ρ , we can write;

$$\delta E = 0 = \int d\mathbf{r} \left[V(\mathbf{r}) + \frac{\delta T}{\delta \rho(\mathbf{r})} + \frac{\delta E_{ee}}{\delta \rho(\mathbf{r})} \right] \delta \rho(\mathbf{r}). \quad (2.10)$$

According to the law of conservation of mass (in this case the number of particles), it is necessary that we have;

$$\int d\mathbf{r} \delta \rho(\mathbf{r}) = 0. \quad (2.11)$$

Handle the constant-number constraint by Lagrange undetermined multiplier, and get;

$$V(\mathbf{r}) + \frac{\delta T}{\delta \rho(\mathbf{r})} + \frac{\delta E_{ee}}{\delta \rho(\mathbf{r})} = \mu, \quad (2.12)$$

where μ is the undetermined multiplier and represents the chemical potential of the system. We can sum up the electron-electron repulsion potential term $\left(\frac{\delta E_{ee}}{\delta \rho(\mathbf{r})}\right)$ and the electron-nucleus attractive potential term $V(\mathbf{r})$ to get the overall potential $V_{\text{eff}}(\mathbf{r})$;

$$V(\mathbf{r}) + \frac{\delta E_{ee}}{\delta \rho(\mathbf{r})} = V_{\text{eff}}(\mathbf{r}). \quad (2.13)$$

Substituting equation 2.13 into equation 2.12, we can write;

$$V_{\text{eff}}(\mathbf{r}) + \frac{\delta T}{\delta \rho(\mathbf{r})} = \mu. \quad (2.14)$$

This is Euler equation for non-interacting electrons in potential $V_{\text{eff}}(\mathbf{r})$, and must be exactly equivalent to Schrödinger equation:

$$\left[-\frac{\hbar^2}{2m_e} \nabla^2 + V_{\text{eff}}(\mathbf{r}) \right] \psi_i(\mathbf{r}) = \varepsilon_i \psi_i(\mathbf{r}), \quad (2.15)$$

where the term in squared brackets is the Hamiltonian operator, ψ_i is the Kohn-Sham orbitals (related with the electron density through equation 2.3) with their corresponding energies ε_i ; the effective potential (V_{eff}) is given by the expression;

$$V_{\text{eff}}(\mathbf{r}) = V(\mathbf{r}) + \int \frac{\rho(\mathbf{r}_2)}{|\mathbf{r}_1 - \mathbf{r}_2|} d\mathbf{r}_2 + V_{\text{xc}}(\mathbf{r}), \quad (2.16)$$

where V_{xc} is the external potential given as the derivative of E_{xc} with respect to the electron density;

$$V_{XC} = \frac{\delta E_{XC}}{\delta \rho}. \quad (2.17)$$

In order to obtain V_{XC} , the E_{XC} functional has to be known. However, it is not known; even if it was known, it might be complicated to solve. Therefore, density functionals with expressions involving the standard functions and mathematical operations are approximated to solve the exchange–correlation energy term. The $E_{XC}[\rho]$ functional has a mathematical form of;

$$E_{XC}[\rho] = E_X[\rho] + E_C[\rho], \quad (2.18)$$

where E_X is the exchange energy functional and E_C is the correlation energy functional terms. The E_X energy term constitutes the largest part of E_{XC} energy term while the E_C energy term constitutes the smallest part of the E_{XC} energy term [92, 93].

The exchange energy term is built from Kohn-Sham doubly occupied orbitals and it has a mathematical expression of [93];

$$E_X^{\text{exact}}[\rho] = -\frac{1}{2} \iint \sum_{\mathbf{k}, j=1}^N \frac{\phi_{\mathbf{k}}(\mathbf{r}_1) \phi_{\mathbf{k}}^*(\mathbf{r}_2) \phi_j(\mathbf{r}_1) \phi_j^*(\mathbf{r}_2)}{\mathbf{r}_1 \mathbf{r}_2} d\mathbf{r}_1 d\mathbf{r}_2. \quad (2.19)$$

The exact exchange energy (E_X^{exact}) formula is similar to that of the Hartree Fock exchange energy for a closed system [93]. Although E_X^{exact} is exactly known, the summation of E_X^{exact} and standard E_C results in poor accuracy in most molecular properties calculations, therefore, approximations are still implemented in solving the exchange term in order to bring about improvement in the results of the calculations [92–100]. The approximations are introduced through the inclusion of the exchange–correlation hole. Exchange–correlation hole is a term utilised to describe a region of space around an electron (at position $\mathbf{r}_1$) in which the probability of finding another electron (at position $\mathbf{r}_2$) is close to zero due to the effects of *electron correlation*. The exchange–

correlation energy term can then be thought as the Coulombic interaction between an electron at $\mathbf{r}_1$ and the surrounding exchange-correlation hole charge $\rho_{xc}(\mathbf{r}_1, \mathbf{r}_2)$, so that equation 2.19 transforms into [101–104];

$$E_X[\rho] = \frac{1}{2} \iint \frac{\rho(\mathbf{r}_1)\rho_{xc}(\mathbf{r}_1, \mathbf{r}_2)}{|\mathbf{r}_1 - \mathbf{r}_2|} d\mathbf{r}_1 d\mathbf{r}_2. \quad (2.20)$$

We can separate the two integrals and write;

$$E_X[\rho] = \frac{1}{2} \int \rho(\mathbf{r}_1) d\mathbf{r}_1 \int \frac{\rho_{xc}(\mathbf{r}_1, \mathbf{r}_2)}{|\mathbf{r}_1 - \mathbf{r}_2|} d\mathbf{r}_2. \quad (2.21)$$

The denominator of the exchange correlation term in equation 2.21 suggests that hole charge at $\mathbf{r}_2$ is not static but depends on the current position of the electron $\mathbf{r}_1$. The term $\rho_{xc}(\mathbf{r}_1, \mathbf{r}_2)$ can be divided into two components; the exchange hole (ρ_x) and the correlation hole (ρ_c);

$$\rho_{xc}(\mathbf{r}_1, \mathbf{r}_2) = \rho_x(\mathbf{r}_1, \mathbf{r}_2) + \rho_c(\mathbf{r}_1, \mathbf{r}_2). \quad (2.22)$$

The exchange energy functional corresponding to the exchange hole is given by the expression;

$$E_X[\rho] = \frac{1}{2} \iint \frac{\rho(\mathbf{r}_1)\rho_x(\mathbf{r}_1, \mathbf{r}_2)}{|\mathbf{r}_1 - \mathbf{r}_2|} d\mathbf{r}_1 d\mathbf{r}_2. \quad (2.23)$$

The correlation energy functional corresponding to the correlation hole is given by the expression;

$$E_C[\rho] = \frac{1}{2} \iint \frac{\rho(\mathbf{r}_1)\rho_c(\mathbf{r}_1, \mathbf{r}_2)}{|\mathbf{r}_1 - \mathbf{r}_2|} d\mathbf{r}_1 d\mathbf{r}_2, \quad (2.24)$$

The exact exchange hole is obtained when substituting equation 2.23 into equation 2.19;

$$\rho_x(r_1, r_2) = -\frac{2}{\rho(r_1)} \sum_{k,j=1}^N \phi_k(r_1) \phi_k^*(r_2) \phi_j(r_1) \phi_j^*(r_2) dr_1 dr_2. \quad (2.25)$$

However, the exact correlation hole is not known; therefore, the exact form of the E_C is not known and has to be approximated. In order to find the exact correlation hole term inside the E_C term and also to approximate the E_X term even though it is known, DFT functionals are utilised. In fact, DFT approximates both the E_X and the E_C energy terms inside the E_{XC} term. The next section explains some of the approximation approaches utilised to estimate the E_{XC} term.

2.1.2 Approaches for approximating the exchange-correlation term

The DFT functionals used to approximate the exchange-correlation energy term may be constructed through the use of different approaches [92, 93], including

- local density approximation,
- low order density-gradient expansion,
- high order density-gradient expansion and
- hybrid density functional methods.

Local density approximation (LDA): LDA describes an electron density for a homogeneous electron gas. A homogenous electron gas system is a quantum chemical system with a finite density consisting of many interacting electrons in an infinite volume [92–98]. In the LDA, the exchange correlation (XC) energy density of a system at a point $\mathbf{r}$ reads:

$$E_{XC}^{LDA}[\rho](\mathbf{r}) = E_{XC}^{HEG}(\rho(\mathbf{r}))$$

where $E_{XC}^{HEG}(\rho(\mathbf{r}))$ is the XC energy density of the homogenous electron gas (HEG) having the electron density $\rho(\mathbf{r})$ of the studied system at $\mathbf{r}$.

If the properties of a homogenous electron gas are known, the electron density of a molecule can be divided into small segments; each segment can be treated as a homogenous electron gas. The overall LDA exchange-correlation term can be evaluated as a sum of the exchange term and the correlation energy term expressions. The mathematical expression for the exchange energy term part of the LDA is modelled to indicate a slowly varying charge-density distribution at a given point [93, 95, 97];

$$E_X^{LDA} = -C_X \int \rho^{\frac{4}{3}}(\mathbf{r}) d\mathbf{r}, \quad (2.26)$$

where C_X is a constant and is given by;

$$C_X = \left(\frac{3}{4} \right) \left(\frac{3}{\pi} \right)^{\frac{1}{3}}. \quad (2.27)$$

The correlation energy per electron (for a uniform electron gas) is given through the expression [93, 97];

$$E_C^{LDA} = -A \int \rho(1 + \alpha_1 r_s) \ln \left[1 + \frac{1}{A \left(\beta_1 r_s^{\frac{1}{2}} + \beta_2 r_s + \beta_3 r_s^{\frac{3}{2}} + \beta_4 r_s^2 \right)} \right] d\mathbf{r}, \quad (2.28)$$

where $r_s = \left(\frac{3}{4\pi\rho} \right)^{\frac{1}{3}}$ and A , α and β are fixed parameters. The summation of E_X^{LDA}

(equation 2.26) and E_C^{LDA} (equation 2.28) gives a reasonable approximation for the exchange–correlation term in the limit of high and low density. LDA works remarkably well in describing covalent bonds, metallic bonds, ionic bonds and lattice constants especially when compared to Hartree Fock method [97, 98]. However, it gives poor description of hydrogen bonds, underestimate ionization energies and overestimate binding energies and barrier height energies.

Low order density-gradient expansion: it is an approach that improves LDA by considering a real system with inhomogeneous electron density (i.e., slowly varying electron densities [95, 96, 103, 104]) rather than a homogenous system with constant electron density. This approach approximates the exchange-correlation energy functional based on electron density ρ and its gradient $\nabla\rho$ or gradient modulus $|\nabla\rho|$;

$$E_{xc}^{GGA}[\rho] = \int \rho(\mathbf{r}) \varepsilon_{xc}(\rho(\mathbf{r}), |\nabla\rho(\mathbf{r})|) d\mathbf{r}. \quad (2.29)$$

The first attempt to improve the LDA approach is to invoke a density function ($\mu\rho$) which reduces the exchange constant component (C_x) in equation 2.26 [92–95];

$$E_{xc}[\rho] = \int \varepsilon_{xc}^{LDA}(\rho(\mathbf{r})) [1 + \mu(\rho)s^2 + \dots] d\mathbf{r}, \quad (2.30)$$

where $\varepsilon_{xc}^{LDA}(\rho(\mathbf{r}))$ is the exchange-correlation energy density and the reduced density gradient s is given by the expression;

$$s = \frac{|\nabla\rho|}{\rho^{\frac{3}{4}}}. \quad (2.31)$$

The main shortcoming of density gradient is that the addition of $\mu\rho s^2$ to LDA equation results in positive correlation energy [93, 97, 99]. An attempt used to overcome density gradient limitation, is to replace the square brackets in equation 2.30 with the enhancement factor F_{xc} that describes the approximation for exchange-correlation contribution to the total energy. The exchange-correlation energy in equation 2.30 becomes;

$$E_{xc}^{GGA} = \int \varepsilon_{xc}^{LDA}(\rho) F_{xc}(\rho, s) d\mathbf{r}. \quad (2.32)$$

Approximated functionals obtained using equation 2.32 are called generalised gradient approximation (GGA). The F_{xc} functional differs for different functionals approximated;

for instance, the F_{xc} functional for the Perdew-Burke-Enzerhof (PBE) functional has a mathematical form;

$$F_{xc} = 1 + \frac{as^2}{1 + bs^2}, \quad (2.33)$$

while the F_{xc} functional for the Becke's 1998 exchange functional (B88) has the form;

$$F_{xc} = 1 + \frac{as^2}{1 + bs \ln \left(s + \sqrt{1 + as^2} \right)}, \quad (2.34)$$

where a and b are just constants obtained from the properties of $E_x[\rho]$ or are fitted in experimental findings. The GGA functionals have considerable advantages compared to LDA and Hartree Fock approaches; they provide improved description of geometric parameters, energetic parameters and significantly describes hydrogen bonds and other weak bonds. However, they are unable to solve the self-interaction error resulting from artificial interaction of the electron density in one-electron system [93–96, 103, 104].

High order density-gradient expansion: Functionals that contains additional semilocal information beyond the first-order density gradient $[\nabla \rho(\mathbf{r})]$ are referred to as high order density-gradient expansion functionals. They are commonly termed as meta-GGA (M-GGA) functionals [105–112]. The lowest high-order density gradient expansion corresponds to the second-derivative of the density, which can be modelled as a Laplacian of the density $[\nabla^2 \rho(\mathbf{r})]$. In practice however, the high order derivatives (such as the Laplacian of the density) are replaced with the kinetic energy density terms, which involves derivatives of the occupied Kohn-Sham orbitals, that are considered to be more numerically stable than the high order derivative terms of the density. For instance, the Laplacian of the density is often replaced by the second derivative of the occupied Kohn-Sham orbitals, which is given by the expression;

$$\tau[\rho] = \frac{1}{2} \sum_{i=1}^{\text{occ}} |\Delta \psi_i(\mathbf{r})|^2. \quad (2.35)$$

In this way, the mathematical expression for the meta-GGA functionals has the form;

$$E_{XC}^{M-GGA}[\rho] = \int \varepsilon_{XC}(\rho(\mathbf{r}), \nabla\rho(\mathbf{r}), \tau(\mathbf{r})) d\mathbf{r}. \quad (2.36)$$

Meta-GGA methods represent a significant improvement in the determination of properties such as atomization energies. However, they are more technically challenging, with several difficulties in terms of numerical stability. M-GGA functionals can be designed to be either exclusively exchange functional or exclusively correlation functional. Examples of exchange M-GGA functionals include Tao, Perdew, Staroverov and Scuseria functional (TPSS), modified Becke-Johnson (MBJ) and an example of correlation M-GGA functional is Becke 1996 (B96) [105, 109, 110].

Hybrid density functional methods: methods in which the exchange term, in the exchange-correlation term, is modelled as a mixture of the exact exchange functional (E_X^{exact}) and the semilocal density functional approximations (E_X^{DFT}) are known as hybrid generalised gradient functionals (hybrid-GGA [113–117]);

$$E_{XC} = a E_X^{\text{exact}} + (1-a) E_X^{\text{DFT}} + E_C^{\text{DFT}}, \quad (2.37)$$

where E_X and E_C are exchange and correlation GGAs respectively, E_X^{exact} is the nonlocal exact exchange (Hartree Fock exchange energy); a is a mixing fraction obtained from empirical fitting and its value is within the range $0 \leq a \leq 1$. In this way, hybrid-GGAs are designed from inclusion of empirical data rather than using many constraints.

There are different types of hybrid-GGA functionals including; global hybrid functionals and local hybrid functionals. Global hybrid functionals are developed based on an approximation that the value of a is a constant and independent of density, density gradient and position $\mathbf{r}$. An example of global hybrid functional is Becke's three-parameter-Lee Yang Parr (B3LYP [117–122]). It has mathematical form involving addition of new parameters to equation 2.37;

$$E_{XC} = a E_X^{\text{exact}} + (1-a) E_X^{\text{LDA}} + a_x \Delta E_X^{\text{B88}} + E_C^{\text{LDA}} + a_c E_C^{\text{GGA}}, \quad (2.38)$$

where a , a_x and a_c are numerical parameters obtained from empirical fitting and have values 0.2, 0.72 and 0.81 respectively. This functional results in accurate findings that are close to the experimental data than the meta-GGA functionals. It became one of the most popular since its development and it is still used [105, 116–120]. The successful application of B3LYP led to the expansion of this approach by designing new global hybrid functionals such as Becke 1995 (B95). Although B3LYP functional gained a lot of attention, it is unable to solve self-interaction error while considering non-dynamic correlation simultaneously.

Other well known and utilised global hybrid functionals include the Becke half-half Lee Yang Parr (BHHLYP), Minnesota meta hybrid functional (M06–2X) with 54% HF exchange (having twice the HF exchange percentage of M06 functional) and modified Perdew-Wang 1-parameter for kinetics (MPW1K), which has 42.8% HF exchange [102, 115–122]. The BHHLYP is constructed in such a manner that it contains 50% HF-like exchange, 50% Becke 88 exchange and 100% LYP correlation functional;

$$E_{\text{BHHLYP}} = 0.5 * E_X^{\text{exact}} + 0.5 * E_X^{\text{B88}} + 1.0 * E_C^{\text{LYP}}. \quad (2.43)$$

These functionals provide good accuracy for transition metals, thermochemistry and kinetics. For these reasons, BHHLYP, M06–2X and MPW1K hybrid functionals were selected for utilisation in the study on the reaction mechanisms of phloroglucinol derivatives with radical species, the results of which are reported in this dissertation.

The local hybrid functionals are developed from an approximation that the value of a spatially depends on position r . Its mathematical form is expressed as [93];

$$E_X = \sum \int \{g_\sigma(\mathbf{r}) \varepsilon_X^{\text{exact}}(\mathbf{r}) + [1 - g_\sigma(\mathbf{r})] \varepsilon_X^{\text{DFT}}(\mathbf{r}) d\mathbf{r}\} + E_C^{\text{DFT}}, \quad (2.39)$$

where $g_{\sigma}(\mathbf{r})$ is a local mixing function that has an expression involving the von weizsäcker kinetic energy in equation 2.39.

$$g_{\sigma}(\mathbf{r}) = a \frac{\tau_{\sigma}(\mathbf{r})}{\tau_w(\mathbf{r})}, \quad (2.40)$$

where von Weizsäcker kinetic energy density is expressed as;

$$\tau_w = \frac{|\nabla \rho_{\sigma}|^2}{8\rho_{\sigma}}. \quad (2.41)$$

The kinetic energy density involving the Kohn Sham orbitals has a mathematical form;

$$\tau_{\sigma}[\rho_{\sigma}] = \frac{1}{2} \sum_{i=1}^{\text{occ}} |\Delta \psi_{i\sigma}(\mathbf{r})|^2, \quad (2.42)$$

where σ is the spin density. The g_{σ} function controls the extent of the exact exchange and the meta-GGA functionals present in equation 2.40.

2.2 Solvation and solvation models

2.2.1 Solvation process

Solvation is a process of transferring a molecule from gas phase (which has a dielectric constant of 1) to a condensed phase (which has a dielectric constant greater than 1). The molecule that is being transferred from the gas phase to the condensed phase is called a solute. The condensed phase into which the molecule is transferred to is usually a solvent [123, 124]. In this way, a solute is a molecule that is embedded in the solvent and the solvent is a medium that dissolves a solute; for this reason, the solvation process is also commonly referred to as dissolution process. The outcome of the interaction of the solvent

and the solute molecule is the formation of a solution. The solute molecule can exist in a solid, liquid or gas state, while the solvent preferably exists in either a liquid or gas state. When the solvent and the solute are in a liquid state, the strongest interaction between the species are observed when both solute and solvent molecules are either polar in nature or non-polar in nature, which is consistent with the empirical rule that *like dissolves like* (i.e., a polar solute molecule is likely to dissolve in a polar solvent [125, 126]).

The solvation process involves a number of steps, which include the formation of the cavity with the solvent to accommodate the solute, polarisation of the solvent molecules by the solute molecule and the formation of interaction forces between the solute and the solvent molecules [124, 127–132]. The availability of the space within the solvent to accommodate the solute is a necessary step in the process of transferring the solute into the solvent. The space into which the solute would be accommodated by the solvent is known as the cavity. The creation of the cavity within the solvent is an energy requiring process and corresponds to a destabilisation factor. When the solute molecule enters the solvent, the molecules of the solvent reorient in order to accommodate the solute and in the process solvent molecules are polarised by the solute charge density [124–136]. Solvent polarisation is the process in which the electron cloud of the solvent is distorted by the external electric charge [133–136], in this case, the charge density of the solute. In turn, the solvent molecules polarise the solute molecule as well. The polarisation of the solute by the solvent and the polarisation of the solvent molecules by the solute molecule results in the release of energy [135, 136]. The presence of the solute within the solvent may also involve the formation of intermolecular interactions between the solvent and the solute molecule. These forces can either be long-range or short-range type of electrostatic interactions. A short-range force is an electrostatic attractive force that forms when the two oppositely charged particles (nuclei and electron) are close to each other (less than 3 Å [137]). Examples of short-range forces are hydrogen bonds which may form between the two interacting molecules. A long range force is an electrostatic attractive or repulsive force that forms when the oppositely charged particles interact from a distance of greater than 3 Å (e.g., dipole-induced dipole interaction, charge dipole interactions and induced dipole-induced dipole interaction [138]). The interaction between a solute and solvent molecules is a favourable process resulting in lowering of the energy of the system. The

energy of the system is determined by the energy at the establishment of solute...solute ($A\cdots A$) interactions, solvent...solvent ($B\cdots B$) interactions and solute...solvent ($A\cdots B$) interactions. The breaking of the $A\cdots A$ interactions requires energy (for breaking the relevant intermolecular bonds between solute molecules); moreover, an amount of energy is also needed for breaking some $B\cdots B$ interactions (for breaking the relevant intermolecular bonds between the solvent molecules). However, energy is released when A and B interacts (for the formation of the intermolecular bonds between A and B). If the energy required for breaking the $A\cdots A$ and the $B\cdots B$ interactions is less than the energy released when $A\cdots B$ interaction is established, then it can be concluded that the solvation process is thermodynamically favoured. The thermodynamic parameters such as the overall enthalpy for the solvation process (ΔH_{sol}) is defined by the sum of the change in enthalpy at $A\cdots A$ interaction ($\Delta H_{A\cdots A}$), change in enthalpy at $B\cdots B$ interaction ($\Delta H_{B\cdots B}$) and change in enthalpy at $A\cdots B$ interaction ($\Delta H_{A\cdots B}$);

$$\Delta H_{\text{sol}} = \Delta H_{A\cdots A} + \Delta H_{B\cdots B} + (\Delta H_{A\cdots B}). \quad (2.44)$$

In solvation process, the internal energy of the system decreases (energy is released by the system to the surroundings). There is also an increase in the disorder of the system due to the dispersion of solvent molecules when the cavity is created within the solvent. The two energy terms can be combined together through the use of the Helmholtz equation and taking into consideration the energy differences;

$$\Delta A = \Delta U - T\Delta S, \quad (2.45)$$

where A is Helmholtz free energy, T is the absolute temperature, S is the entropy of the system and U is the internal energy for the system at constant temperature or volume [139, 140]. If we consider a more practical situation in which the system is considered to be at constant pressure, it is possible to express the amount of heat transferred into the system in terms of enthalpy instead of internal energy through the relationship;

$$\Delta H = \Delta U + P\Delta V. \quad (2.46)$$

It is also possible to express the overall change in free energy of the system in terms of Gibbs free energy (G) instead of Helmholtz free energy, so that we can write;

$$\Delta G = \Delta H - T\Delta S, \quad (2.47)$$

where H and S represent enthalpy and entropy of the system respectively and T represents the absolute temperature. ΔG (change in Gibbs free energy) must be negative for solvation process to occur.

The contributing factors to the overall Gibbs free energy of solvation include the Gibbs free energy change due to polarisation, which is an electrostatic effect that is represented with an energy term ΔG_{elec} ; dispersion Gibbs free energy that is denoted as ΔG_{disp} and the cavitation Gibbs free energy term that is denoted as ΔG_{cav} . In this way, the overall solvation energy (ΔG_{solv}) is written as;

$$\Delta G_{\text{solv}} = \Delta G_{\text{elec}} + \Delta G_{\text{disp}} + \Delta G_{\text{cav}}. \quad (2.48)$$

Solvation process is possible if the sum of the energy resulting from electrostatic interaction and dispersion is greater than the energy required for the cavity formation.

The ΔG_{elec} is a result of the solute-solvent effects and therefore it is evaluated as the difference between the Gibbs free energy of the solute *in vacuo* ($\Delta G_{\text{ele,vac}}$) and in the Gibbs free energy of the solute in solution ($\Delta G_{\text{ele,sol}}$);

$$\Delta G_{\text{ele}} = \Delta G_{\text{ele,sol}} - \Delta G_{\text{ele,vac}}. \quad (2.49)$$

The type and strength of solute-solvent interaction depends on the nature of the solute and the solvent [136, 141]. The solute-solvent interactions are electrostatic in nature and can be either long range or short range in character. The effect of the solvent on the solute molecule can be assessed more appropriately by taking into consideration the bulk solvation effect rather than individual solvent molecules [123, 136, 141]. The solvent may affect some of the parameters of the solute, such as the geometry, the atomic charges,

dipole moment, vibrational frequency, electronic transition energies and chemical reactivity [136, 140, 141]. For instance, the solute molecule in the gas phase tends to undergo geometry distortion (e.g., bond elongation) or separation of charge distribution, when it is transferred into the solvent, in order to allow better interaction with the solvent molecules [136, 141]. The distortion on the solute molecule is an energy requiring process resulting in an increase in the enthalpy of the system, then the solute polarises the surrounding solvent, rising its Gibbs free energy. The extent of the solute polarisation by the solvent depends on the solvent dielectric constant; it is greater when the dielectric constant of the solvent is greater than 1. The more polar the solvent is, the higher is its dielectric constant [141–143]. For instance, water, ethanol and benzene molecules have dielectric constants of 78.39, 24.5 and 2.27, respectively [141–144]. Therefore, water molecules (solvent) are expected to polarise a solute molecule more than ethanol and benzene solvent molecules.

Solvent effects on the solute molecule such as bond elongation and bond contraction are caused by the presence of intermolecular hydrogen bonds (H-bonds) that may form when a solute molecule interacts with solvent molecules. Not all molecules can form H-bonds; but a H-bond can be formed between one molecule consisting of an atom that is a hydrogen atom acceptor (Lewis base) and another molecule consisting of an atom that is a hydrogen atom donor (Lewis acid). Solute-solvent interactions may result in several H-bonds depending on possible sites for $A-H\cdots B$, where A and B are highly electronegative and H is a hydrogen atom. Solvent molecules may also form H-bond with each other (i.e., when a bulk of water molecules are used as a solvent). Strong solvent solute interactions are obtained when a system consist of H-bonds [145–148].

The solute molecule may have different conformational features when comparing the geometry in gaseous phase and the geometry in condensed phase, especially when it is dissolved in a solvent with high dielectric constant (such as water). Conformational changes within the solute molecule, just as bond elongations, may also be accounted for by electrostatic interactions between the solute and the solvent molecules; polar solvents have greater effect to cause conformational modifications (i.e. , changes in the torsion angles between the geometry of the solute in the gas phase and the geometry of the solute

in the condensed phase) than non-polar solvents; this is due to the fact that polar solvent may form H-bonds when interacting with an organic solute molecule that possess hydrogen bond donor or acceptor atoms whereas non-polar solvent may form dispersion interaction (e.g., π - π interactions) when interacting with an organic solute [149–151].

ΔG_{disp} is a result of the formation of an instantaneous dipole moment once the solute molecule is inserted in the solvent. When the solute is inserted in a cavity inside a solvent, the solvent molecules reorient, changing the directions of the dipoles of the solute. However, the induced solute dipole moment does not depend largely on the solvent dipole moment but rather on the solvent polarity and the solvent dielectric constant [152–155]. This type of long range interaction is called dipole- induced dipole interaction. Dispersion interactions are forces in which temporary dipoles can be induced in two interacting molecules [138, 152]. They may form as a result of an interaction between a non-polar solute molecule and a nonpolar solvent or a polar solute molecule interacting with a polar solvent). A pair of non-polar or polar species may interact as a result of fluctuations in their electron densities [138, 152]. These interactions may also results in a change in solute molecule dipole moment. The reason for the fluctuations in the dipole moment is a result of the fact that the electron clouds of a solute molecule and solvent molecules are distributed unsymmetrically and closer to the nucleus. Solvent molecules get instantaneous dipole. This instantaneous dipole generates electric fields that polarises the solute molecule and induces dipole moment in it [138, 152]. Examples of dispersion forces are π - π interactions, $\text{CH}\cdots\pi$ interaction (which may form, for instance, when a benzene solute molecule interacts with a benzene solvent [150, 151]). The strength of the dispersion force depends on the amount of polarisation on a solute molecule by a solvent.

ΔG_{cav} is one of the non-electrostatic interaction (it does not involve the solute-solvent interaction) components in ΔG_{solv} . Cavity formation is an endothermic process; therefore ΔG_{cav} is a destabilizing factor in solvation. There are two processes in solvation involving the cavity, the first process is the formation of the cavity for a solute molecule; the second process is the insertion of solute in the cavity inside the solvent. The balance between the reversible work of these two processes results in the overall cavitation energy. ΔG_{cav} is a function of the size and shape of the cavity that is created [136].

Solvation process is possible if the sum of the energy resulting from electrostatic interaction and dispersion is greater than the energy required for the cavity formation. In order to obtain information on the solvent effect on the geometry, charge distribution and dipole moments of the solute molecule as well as determining solvation Gibbs free energy of the system, various solvation models methodologies have been developed. The capability of the different solvation models to accurately estimate the solute-solvent effects on the geometry and electronic parameters as well as to determine solvation Gibbs free energy depends on the ability of these models to describe all the main features associated with the solute cavity (e.g., cavity size and shape), charge distribution of the solute and the way in which the media is represented. The next section provides information on the main characteristics of solvation models and also gives a few examples of commonly utilised solvation models implemented in different computational chemistry software programs.

2.2.2 Explicit and implicit representation of the solvent

Solvation models are computational chemistry simulation approaches that are designed to account for the various electrostatic and non-electrostatic interactions that may exist between a solute molecule and the surrounding solvent molecules in order to obtain information on the effect of the solvent on the molecular structure, energetics, spectra, interaction potential and dynamics [136, 152–179]. Solvation models can be subdivided into those that explicitly include the solvent molecules and those that implicitly represent the solvent through the reaction field [146, 152–178].

Explicit solvation model considers interactions between a limited number of solvent molecules in interaction with the solute molecule. The number of solvent molecules included would depend on the accuracy of the results desired; the greater the number of the solvent molecules included the higher is the accuracy of the results. However, an increase in the number of solvent molecules entails an increase in the computational cost. Therefore, the extent of solvent molecules to be included explicitly largely depends on the balance between desired accuracy and computational cost. In some cases, the solvent molecules may only be included in the region of interest around the solute molecule while

the rest of the solute molecule is left non-interacting with the solvent molecules. In such systems, an increasing number of solvent molecules may be investigated interacting with the solute molecule; for instance, the study may consider a solute molecule interacting separately with one, two, three, four or five number of solvent molecules (Figure 2.1). The cut-off value for the number of water molecules to be included in the calculation is

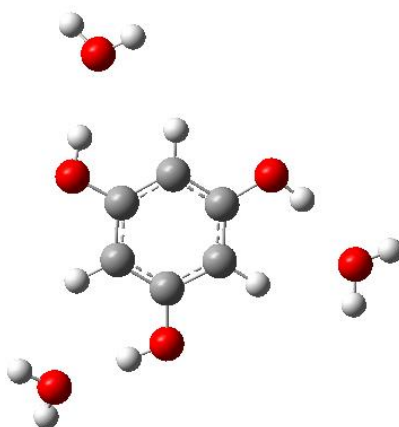


Figure 2.1: Diagram representing a supermolecular system consisting of a solute molecule (phloroglucinol) surrounded by three explicit water molecules [146].

largely determined by the computational cost. A system consisting of the solute and a limited number of water molecules is often referred to as a supermolecular system.

The Gibbs free energy of solvation for the system modelled through explicit consideration of the solvent molecules includes the electrostatic terms that arise as a result of polarisation and dispersion interactions and excludes the non-electrostatic terms such as cavitation energy because in such systems, there is no requirement for the formation of the cavity (since the solvent is not continuous). Therefore, the only contributing components to the overall solvation Gibbs free energy are the electrostatic terms arising from solute-solvent interactions. The Gibbs free energy of solvation for a system that include explicit solvent consideration is estimated as the energy difference between the energy of the interacting species (i.e., solute and solvent molecules) and the total energy of the separate species. In this way we can write;

$$\Delta G_{\text{solv}} = G_{\text{sol-solv}} - (G_{\text{sol}} + G_{\text{solv}}), \quad (2.50)$$

where G_{sol} is the Gibbs free energy of a solute molecule, G_{solv} is the Gibbs free energy of the solvent molecules and $G_{\text{sol-solv}}$ is the Gibbs free energy of the solute-solvent interaction.

However, if the solute molecule or the solvent molecules, interacting with the solute, undergo geometric distortions during the interactions, then an extra energy term accounting for the distortion (G_{dist}) has to be included in equation 2.50, so that, for molecules that are highly flexible (i.e., molecules with a significant number of single rotatable bonds) we can write;

$$\Delta G_{\text{solv}} = G_{\text{sol-solv}} - (G_{\text{sol}} + G_{\text{solv}}) - G_{\text{dist}}. \quad (2.51)$$

Explicit solvation models utilise purely quantum mechanical methods, molecular dynamics or the hybrid of molecular quantum chemical methods (QM) and molecular mechanics (MM) – often denoted as QM/MM approaches, to estimate the Gibbs free energy of solvation by simulating solute-solvent interactions present in the system. When pure QM methods, such as HF, DFT and MP2 are utilised, the number of solvent molecules included as part of the supermolecule is the least because the simulations required in solving the Schrödinger equation becomes computationally demanding. When pure molecular dynamics approaches are utilised, the number of solvent molecules that can included in as part of the supermolecule is the highest because molecular dynamics approaches are largely molecular mechanics type of approaches, which only function by defining an empirical interaction potential called force field. A force field is defined as a collection of force constants over a particular area of space [180]. Examples of force fields that may be used to describe a solute molecule include Assisted Model Building with Energy Refinement (AMBER) and Chemistry at Harvard Macromolecular Mechanics (CHARMM). However, although molecular mechanics approaches are able to determine the interaction potential for a supermolecular system, they do not account for solute polarisable effects [180, 181]. Therefore, for a large system consisting of the solute and numerous solvent molecules, it is preferable that the solute and the solvent molecules, in

immediate region of the solute (i.e., interacting with the solute in the region of the first solvation layer) are treated quantum mechanically while the solvent molecules further away from the solute are treated through the use of molecular mechanics approaches. The utilisation of the QM/MM approaches findings numerous applications in cases in which large solvent molecules have to be included in the supermolecule. QM/MM is designed in such a way that it overcomes the limitations of using QM alone (when treating a supermolecular system with a large number of solvent molecules) and the limitations associated with MM approaches (i.e., the problem of not accounting for solute polarisable effect in a supermolecular system [182]). Another way to use QM/MM method in solvated systems is through the use of QM method at the active site of a solute molecule whereas the remaining region of a solute is treated using MM method or vice versa [183–186]. QM/MM approach is often used in biological processes including molecular docking and ligand binding. Moreover, application of QM/MM approach is currently expanding to highly diffusive catalysis systems [184, 185].

Implicit solvation model is another quantum mechanical approach designed to treat solvent systems, where the solvent molecules are not explicitly included but are rather represented by the uniform (continuum) polarisable medium having the same dielectric constant as the solvent [136, 162–166]. These approaches do not consider limited number of solvent molecules but rather consider the solvent molecules as bulky and therefore possessing homogenous properties. When a solute is inserted into the continuum polarisation medium (representing the solvent, Figure 2.2), the solute molecule polarises the medium which in turn polarises the solute molecule. The polarisation of the solute molecule depends on the dielectric constant of a continuum medium in which the solute molecule is embedded inside a cavity surrounded by the dielectric medium [136, 162–166]. The primary advantage of a continuum solvation model over explicit solvation model is based on the low computational cost it has due to reduced size of the system.

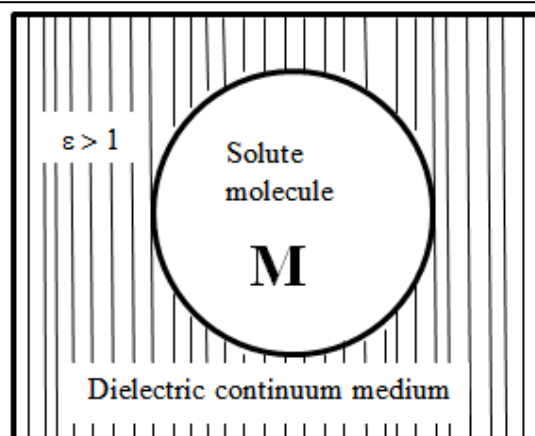


Figure 2.2: Schematic diagram representing solvation process where a solute molecule is inserted in a cavity inside the dielectric continuum medium.

There are different types of solvation models that have been developed to account for the estimation of solute-solvent effects. The various models differ from each other in five different aspects, which are;

- how the dielectric medium is described
- whether the solute **M** is described classically or quantum mechanically
- the creation of the cavity, through consideration of the size and shape of the solute cavity
- how the charge distribution (ρ) of solute **M** is represented
- method of calculating the electrostatic interactions and dispersion contribution

Description of the solvent medium: In continuum solvation models, the solvent is represented as a homogenous (i.e., isotropic) and an infinite (i.e. continuous) medium with a dielectric constant similar to that of a modelled solvent. The electric field for an isotropic medium possessing random motion within the system is zero [186–195]. However, when inserting the solute molecule inside a cavity within a solvent, the charge distribution of a solute molecule polarises solvent molecules resulting in solvent reorientation and the change in electric field so that the overall electric field is non-zero. This non-zero electric field is known as the reaction field. In turn, the solvent polarises a solute molecule, through its reaction fields, resulting in the change in the solute molecular

properties. The dielectric constant (ϵ) for an isotropic continuum media is a scalar permittivity with a magnitude greater than 1. The continuum representation of the solvent approximates linear response of the solvent to the local electric fields;

$$\mathbf{P}(\mathbf{r}) = \chi_e \mathbf{E}(\mathbf{r}), \quad (2.52)$$

where χ_e is the electric susceptibility relating the electric field in the system due to charge distribution. Moreover, the value of polarisation at any point in the solvent is determined by the electric field at that point.

Description of the solute: The solute molecule in implicit solvation model may be described using molecular mechanics or quantum mechanics approaches. In methods utilising MM approaches, atoms of a solute molecule are considered as a set of different charged points linked by springs, resulting in an interaction potential referred to as force fields [190]. Because MM approaches do not take into account the internal features of an atom, its ability to describe the charge distribution of the solute is limited; as a consequence, MM approaches are not be able to capture the solvent polarisation arising from the charge distribution of the solute. In quantum mechanics, the internal components of an atom are taken into consideration. Furthermore, these approaches can account for the solvent polarisation by the charge distribution of a solute molecule which results in inducing reaction fields (i.e., a non-zero reaction field). The reaction field of the system increases the solute polarizability. Examples of QM approaches that may be utilised to describe the solute molecule are HF, DFT and MP2. QM determines the molecular properties of the solute molecule by solving the relevant Schrödinger equation with an appropriate basis set.

Description of the solute cavity: The cavity is used to accommodate a solute molecule inside the continuum dielectric medium. The size and shape of the cavity are very important when designing the cavity. An ideal cavity should

- attempt to reproduce the shape of the solute molecule
- include the whole charge distribution of a solute molecule
- exclude empty spaces which may accommodate solvent molecules

- not be too large or too small (i.e., volume and the surface area) because it may cause serious errors which may arise in the evaluation of the interaction energy in the interface region.

The shape of the created cavity influences the charge distribution of the solute; if the cavity is uniform, the charge distribution is likely to be uniform while if the shape of the cavity is non-uniform, the charge distribution on the solute is preferably non-uniform [196–200]. The shape of the cavity often utilised in implicit solvation models is either spherical or ellipsoidal; it is also described through the use of molecular surfaces. The spherical shaped cavity and the ellipsoidal shaped cavity express the solute charge distribution (ρ_M) in terms of multipolar one-centre expansions of solute-solvent reaction field ($V(\mathbf{r})$) and ρ_M .

When the solute is embedded in a cavity that has either spherical or ellipsoidal shape, the electrostatic interactions are solved using analytical methods such as image charge method (ICM [176]). The description of the solute cavity through consideration of the molecular surfaces is accomplished through the use of solvent accessible surfaces (SAS) and solvent-excluded surfaces (SES). These surfaces allows for the determination of the interaction energy of the solute molecule and an atomic probe (solvent molecule) placed at an appropriate position at the outer molecular space [136, 162–166]. Solvent accessible surface consists of the van der Waals surface of the atoms that are accessible to the probe sphere (contact surface). The closest point of the solvent “probe” describes solvent excluded surfaces as it rolls along the van der Waals spheres (Figure 2.3).

Van der Waals surface

Solvent accessible surface

Solvent excluded surface

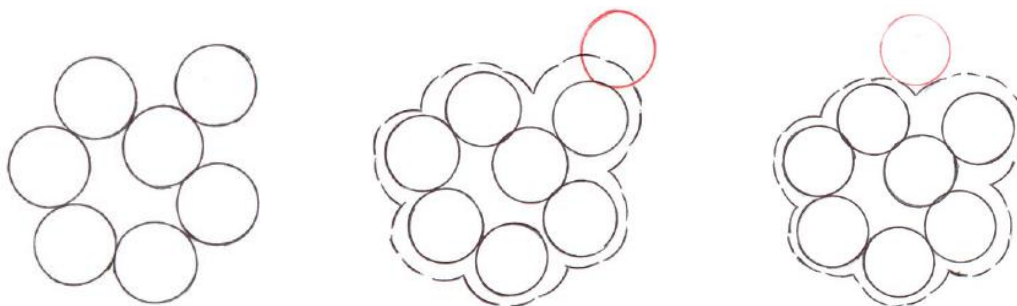


Figure 2.3: Schematic diagrams representing the description of a solute cavity through molecular surfaces. The black coloured spheres represent the overlapping atomic spheres of a solute molecule forming a Van der Waals surface, the red coloured sphere represents a probe (solvent molecule) and the black dashed lines represent the path of a probe as it rolls over the Van der Waals surface resulting in solvent accessible surface and solvent-excluded surface.

Representation of the charge distribution (ρ) of solute in the estimation of the solute-solvent effects: Charge distribution can be modelled through consideration of a charge point inside a cavity whose electric fields penetrate the solvent. This approach is used in generalised Born model of ion solvation [148]. The Born model introduces an arbitrary cavitation when an ideal cavity is not accurate. An arbitrary cavitation is a process of creating a cavity around the solute, having a similar shape as overlapping space-filling atomic spheres. The surface of the sphere is approximated to be entirely smooth; therefore, the charge distribution is expected to be uniform and continuous. The mathematical expression of charge distribution at any point can be written as;

$$\rho(s) = \frac{\rho_M}{4\pi r^2}, \quad (2.53)$$

where s denotes a cavity surface, ρ_M is the charge of a solute molecule and r represents the radius of a sphere.

A second approach of representing charge distribution of a solute molecule within a cavity is using a central dipole instead of a charge point. A dipole is embedded inside an ellipsoidal shaped cavity that is created in a continuum medium. The symmetry of the cavity does not match with the symmetry of the electric fields. In this case, the electric fields of the central dipole are produced in such a way that the cavity polarises the continuum medium, this is called inhomogeneous polarisation resulting in an induced reaction fields in the medium. The reaction fields induced in this way are called the Onsager reaction fields [197, 198].

The solute charge distribution within the cavity may also be modelled by inducing the charge distribution at the cavity surface. This approach is known as apparent surface charge (ASC). In this approach, a cavity is created by a number of overlapping spheres corresponding to the number of atoms forming a Van der Waals surface with specific atomic radii (typically 1.2Å). The cavity is divided into a number of surface elements (ΔS_i) with the solute charge distribution (ρ_{Mi}) at the centre. The charge density at the surface of the cavity $\rho(s)$ is obtained from the electric field generated by the unperturbed solute charge distribution. The equation for determining the induced charge distributions at the cavity surface can be written as;

$$\rho_{Mi} = \rho(s)\Delta S_i. \quad (2.54)$$

When ρ_{Mi} solute charges have been identified, using equation 2.54, they are utilised in the formation of electric fields which results in the formation of new charge distribution at the surface cavity $\rho^0(s)$. This process is repeated until self-consistence (i.e., solvent having time to fully respond to a new solute charge distribution) is achieved [197, 201]. Moreover, the reaction field potential $V(\mathbf{r})$ obtained in this way will be added in the Hamiltonian of a solute molecule. The main shortcoming of this method is caused by the complicated non-uniform shaped cavity having a lot of intersections resulting in slow convergence of numerical integrations. Therefore, methods that employ this approach often use isosurfaces (e.g., Connolly surfaces) in order to overcome the problem. An isosurface is a region having constant electron charge distribution. An isosurface is likely

to change at each cycle of self-consistence (iteration) due to the fact that each iteration updates the solute charge distribution [197].

Calculating the electrostatic interaction contributions: In order to solve the Schrödinger equation for a system in solution, it is necessary to modify the Hamiltonian equation *in vacuo* to include the contribution arising from the solute-solvent interactions. Consider for instance that the Hamiltonian operator in vacuum for a solute is represented with a letter H° . This Hamiltonian operator is only sufficient to describe the properties of the solute. In order to account for the properties arising from the solute-solvent interactions, it is necessary to consider the potential term due to the solute-solvent interactions, it can then be envisaged that such potential, denoted as V_{int} can be added to the Hamiltonian H° (describing the solute), resulting in the overall effective Hamiltonian (H_{eff}) operator [136, 187, 188];

$$H_{\text{eff}} = H^\circ (f) + V_{\text{int}} (f, \mathbf{r}), \quad (2.55)$$

where H° is the solute molecular Hamiltonian, and $V_{\text{int}} (f, \mathbf{r})$ is the sum of the interaction potentials between the solute and the solvent molecules; f represents the set of all the solute coordinates (nucleus and electronic coordinates) and $\mathbf{r}$ represents the set of all the coordinates of the nuclei and electrons within the solvent molecule. The implication of using this kind of an effective Hamiltonian is that there is no need to know all the details about the solvent molecules (i.e., the Hamiltonian of the individual solvent molecules is excluded in the equation) and that the only important information is the description of the interaction between the solute and the solvent. In order to completely eliminate the role of the solvent molecules, it is significant that equation 2.55 should not contain terms that are dependent on the coordinates of the solvent molecules [136, 187]; this is done by introducing the solvent response function, denoted as $S(\mathbf{r}, \mathbf{r}')$,

$$H_{\text{eff}} = H^\circ (f) + V_{\text{int}} (f, S(\mathbf{r}, \mathbf{r}')), \quad (2.56)$$

with $\mathbf{r}$ denoting position vector rather than the whole set of solvent coordinates related to electron and nuclei motions. $S(\mathbf{r}, \mathbf{r}')$ is similar in nature to the response functions that can

be obtained from the electron density function of a single molecule. This case, however, the density that is to be considered is that of the solvent. For this reason, $S(\mathbf{r}, \mathbf{r}')$ is taken as a sum of the separate terms contributing to the different components of the solute-solvent interactions. $S(\mathbf{r}, \mathbf{r}')$ is with respect to an external electric field. Considering that the polarisable density $\mathbf{P}$ in the medium is proportional to the external field ($\mathbf{E}$), we can write;

$$\mathbf{P} = \frac{\varepsilon - 1}{4\pi} \mathbf{E}. \quad (2.57)$$

Although this equation is applicable to different systems, it can be argued that, for a solvated system, the external field ($\mathbf{E}$) can be described as the solvent reaction field [$V_{\text{int}}(\mathbf{r}, S(\mathbf{r}, \mathbf{r}'))$], here represented as the kernel response function of the form $S(\mathbf{r}, \mathbf{r}')$; the permittivity function appearing in the equation can be simple and often represented as a numerical function. The Poisson equation, for a spherical system, can be written as

$$-\nabla[\varepsilon(\mathbf{r}) \nabla \mathbf{V}(\mathbf{r})] = 4\pi\rho(\mathbf{r}), \quad (2.58)$$

where $\varepsilon(\mathbf{r})$ represents the space dependent dielectric permittivity parameter, $\mathbf{V}(\mathbf{r}) \approx 0$ as $r \rightarrow \infty$ and $\rho(\mathbf{r})$ denotes the charge distribution of the solvation system. With an approximation that all charges are found within the cavity [136, 176], the Poisson's equation can be written as;

$$-\nabla^2 V_{\text{total}}(\mathbf{r}) = 4\pi\rho(\mathbf{r}), \quad \text{inside the cavity, where } \varepsilon = 1. \quad (2.59)$$

$$-\varepsilon \nabla^2 V_{\text{total}}(\mathbf{r}) = 0, \quad \text{outside the cavity, where } \varepsilon > 1 \text{ and a finite value} \quad (2.60)$$

where V_{total} is the sum of the electrostatic potential of the system (V_{M} ; generated by ρ_{M}) and reaction potential (V_{R} ; generated by polarisation of dielectric continuum);

$$V_{\text{total}}(\mathbf{r}) = V_{\text{M}}(\mathbf{r}) + V_{\text{R}}(\mathbf{r}). \quad (2.61)$$

Equation 2.59 and 2.60 can be solved by introducing two boundary conditions related to the nature of the potential at infinity and at the surface of the cavity [136, 176, 193, 196]; at infinity, two scenarios can be considered, one in which

$$\lim_{r \rightarrow \infty} rV(\mathbf{r}) = \alpha, \quad (2.62)$$

$$\lim_{r \rightarrow \infty} r^2V(\mathbf{r}) = \beta, \quad (2.63)$$

where α and β are values at infinity, these conditions ensure Harmonic behaviour for solutions. Conditions at the surface of the cavity are referred to as jump conditions; the first jump condition defines the continuity of the electrostatic potential of the system across the surface;

$$[V] = [V]_{\text{in}} - [V]_{\text{out}} = 0, \quad (2.64)$$

where $[V]_{\text{in}}$ and $[V]_{\text{out}}$ are the values of the electrostatic potential at neighbouring points just inside and outside the cavity, respectively. The second jump condition describes the discontinuity of the component of the field, which is expressed as gradient of V , that is perpendicular to the cavity surface.

$$[\partial V] = \varepsilon_0 \left(\frac{\partial V}{\partial \mathbf{n}} \right)_{\text{in}} - \varepsilon \left(\frac{\partial V}{\partial \mathbf{n}} \right)_{\text{out}} = 0, \quad (2.65)$$

where $\frac{\partial}{\partial \mathbf{n}}$ is the derivative in a direction perpendicular to the cavity surface and $\mathbf{n}$ represents the outward pointing vector perpendicular to the cavity surface; ε_0 is the permittivity of space in the cavity and it has a value of 1 while ε is the permittivity of the continuum medium and it has a finite value.

The electrostatic Gibbs free energy (G_{ele}) of the solute charge distribution in an electric field generated by polarized dielectric medium at the position $\mathbf{r}$ is determined as the

integral of the product of the charge density of the solute (ρ_M) and the resultant potential $V_{\text{total}}(\mathbf{r})$;

$$G_{\text{ele,sol}} = \frac{1}{2} \int_v \rho_M(\mathbf{r}) V_{\text{total}}(\mathbf{r}) d\mathbf{r}. \quad (2.66)$$

When the polarisable continuum media polarises a solute molecule, there may be induced charge distribution (ρ_M^{induced}) formed within the system [196], so that the overall charge within the system is given as

$$\rho_{\text{total}} = \rho_M^{\text{vacuo}} + \rho_M^{\text{induced}}. \quad (2.67)$$

In this way, equation 2.66 can be written as;

$$G_{\text{ele,sol}} = \frac{1}{2} \int_v (\rho_M^{\text{vacuo}}(\mathbf{r}) + \rho_M^{\text{induced}}(\mathbf{r})) (V_M(\mathbf{r}) + V_R(\mathbf{r})) d\mathbf{r}. \quad (2.68)$$

The expression for the Gibbs free energy of the solute *in vacuo* ($G_{\text{ele,vac}}$) has the form;

$$G_{\text{elec,vac}} = \frac{1}{2} \int_v (\rho_M^{\text{vacuo}}(\mathbf{r})) V_M(\mathbf{r}) d\mathbf{r}. \quad (2.69)$$

We recall here equation 2.49 for estimating the Gibbs free energy of solvation as the difference between the electrostatic Gibbs free energy for the system in solution and the electrostatic Gibbs free energy for the system *in vacuo*. Taking the difference between equation 2.68 and equation 2.69 we obtain;

$$\Delta G_{\text{ele}} = \frac{1}{2} \int_v (\rho_M^{\text{vacuo}}(\mathbf{r})) V_R(\mathbf{r}) d\mathbf{r} + \frac{1}{2} \int_v (\rho_M^{\text{induced}}(\mathbf{r})) [(V_M(\mathbf{r}) + V_R(\mathbf{r}))] d\mathbf{r}. \quad (2.70)$$

Within a solvated system, all real charges of a solute are found within the cavity while the induced charge is found on the surface of the cavity, where the polarisation effects by the medium are most predominant. If we consider the simplest case in which we assume

the possibility of a rigid charge distribution for the solute, then solvent polarisation on the solute would not lead to any induced field. In other words, the second integral in equation 2.70 can be considered to vanish since the term $\rho_M^{\text{induced}} = 0$. In this way the first integral is the only term contributing to ΔG_{ele} . Therefore, the electrostatic Gibbs free energy term has the form;

$$\Delta G_{\text{ele}} = \frac{1}{2} \int_V (\rho_M^{\text{vacuo}}(\mathbf{r}) V_{\text{r}}(\mathbf{r}) \, d\mathbf{r}. \quad (2.71)$$

2.2.3 Selected solvation models

Continuum models are chosen based on the way in which they represent the solvent, a solute molecule, cavity for a solute molecule, charge distribution of a solute molecule and on how they solve the electrostatic interaction between the solute molecule and the solvent. Three different models, namely Onsager model, polarisable continuum model and solvent model density, have been selected for discussion in order to show the difference and similarities between them.

The Onsager model defines a cavity as a spherical or an ellipsoidal shaped space within the solvent embedding a solute molecule whose charge distribution is modelled as a dipole [197, 198]. The interactions between a dipole and Onsager reaction fields are approximated to be in an analytical form. This model has several advantages including; allowing the geometric parameters (i.e., bond length, bond angle and torsion angle) and dipole moment of the solute molecule to change in the presence of a continuum medium, providing vibrational frequency calculations of solvated molecules when using QM approaches [199, 200]. Although Onsager model has considerable advantages, it has limitations, which include; neglecting estimation of dispersion interactions, inability to reproduce solute-solvent interactions, and neglecting solvent static field effects.

Polarisable continuum model (PCM) describes a cavity as a non-spherical shaped region consisting of interlocking multiple spheres resulting in Van der Waals surfaces. It considers the charge distribution of a solute molecule by using the apparent surface charge approach. The interaction between the apparent surface charge and the solvent reaction

fields can be numerically computed by self-consistent reaction field method. PCM has a number of advantages over the Onsager model, including; providing a more realistic shape of a cavity, taking into account the mutual polarisation between the solute and the polarisable medium and considering dispersion energy in solute molecules having zero dipole moment [197–201]. Although this approach has considerable advantages, it is computationally expensive, arising from complicated realistic cavity made of multiple of interlocking spheres. Nowadays, PCM stands for an acronym for a number of solvation models whose foundational formulation is based on the original PCM version of Tomasi and Miertusi, published in 1981 [136, 193]; some of the members of the PCM group include integral equation formalism (IEF-PCM) and conductor-like screening model (COSMO). The COSMO model represents a solvent as a dielectric continuum medium with a changing dielectric constant, from the specific finite value of ϵ , to $\epsilon = \infty$, which corresponds to that of a conductor. The change in the dielectric permittivity strongly modifies the boundary conditions of the electrostatic problem. To include the effects of the finite values of the dielectric constant of the medium, the ideal unscreened charge distribution ρ^* corresponding to $\epsilon = \infty$ is scaled by a function [193];

$$\rho(s) = f(\epsilon)\rho^*(s), \quad (2.72)$$

where $f(\epsilon)$ is a scaling factor defined as;

$$f(\epsilon) = \frac{\epsilon - 1}{\epsilon + k}, \quad (2.73)$$

where k is typically 0.5, and is different when using different versions of COSMO models, for example it can be different when using conductor-like screening model for modelling real solvents than when using conductor-like screening model for modelling ideal systems. The constant k also depends on the shape of a solute molecule and the charge distribution of a solute molecule.

Solvation model density (SMD) is a model that splits the solvation energy of the system into two main components [177, 202, 203]; the first component is the change in Gibbs

free energy of electronic-nuclear interaction with respect to mutual polarisation in solute-solvent interaction due to reaction fields (ΔG_{ENP}) and the second component to the solvation energy (denoted as G_{CDS} , which stands for the Gibbs free energy arising from the cavitation, dispersion and solvent structure effects) is the contribution due to non-bulk electrostatic contributions (it is a result of Gibbs free energy due to short-range effects in the first solvation sphere and it accounts for the correction in cavitation, changes in dispersion energy and possible changes in solvent structure using geometry-atomic surface tensions [202]). The overall solvation Gibbs free energy can be expressed as the sum of these main components;

$$\Delta G_{\text{solv}} = \Delta G_{\text{ENP}} + G_{\text{CDS}}. \quad (2.74)$$

The ΔG_{ENP} can also be decomposed into two components, which are change in electronic-nucleic interaction energy (ΔE_{EN}) and the Gibbs free energy arising from mutual polarisation during the solute-solvent interactions (G_{P});

$$\Delta G_{\text{ENP}} = \Delta E_{\text{EN}} + G_{\text{P}}. \quad (2.75)$$

The SMD model employs generalised Born model to calculate G_{P} term; where the charge distribution of a solute molecule is represented as a collection of partial point charges [177, 202]. The electrostatic contributions are obtained as a result of a self-consistent reaction field treatment that involves the solution of the nonhomogeneous Poisson equation for electrostatic term. In solving the electrostatic term, the systematically optimised atomic radii are used, which are referred to as intrinsic atomic Coulomb radii in the generalised Born model [177, 202, 203]. The equation for solving G_{P} is written as;

$$G_{\text{P}} = \frac{1}{2} \left(\frac{1}{\epsilon_{\text{b}}} - 1 \right) \sum_k^N \rho_k \gamma_k, \quad (2.76)$$

where ϵ_{b} is the dielectric constant of bulk solvent molecules, N is the total number of atoms, k denotes a label of an atom and γ represents the Coulomb integral solved using intrinsic atomic Coulomb radii. The selection of these Coulomb radii depends on the

representation of the solute charge distribution (i.e., the solute molecule can be modelled as a continuous electronic density (like that utilised in COSMO models) or as consisting of discrete partial atomic charges [177]). In order to obtain G_{CDS} in equation 2.74, the following equation is used [177];

$$G_{\text{CDS}} = \sum_k^N \sigma_k A_k (R, \{R_{Zk} + r_s\}) + \sigma \sum_k^N A_k (R, \{R_{Zk} + r_s\}) \quad (2.77)$$

where σ_k is the atomic surface tension of atom k , σ is the molecular surface tension, A_k is the solvent accessible surface area of atom k , Z is the atomic number of k , R is the atomic van der Waals radii of a solute molecule and r_s is radius of the solvent molecule. The Van der Waals atomic radii (i.e., Bondi's values for the van der Waals radii [204]) are used in determining G_{CDS} instead of intrinsic Coulomb radii used for solution of the bulk electrostatic term. σ_k depends on the geometry of the solute molecule and surface tension coefficients;

$$\sigma_k = f Z_K (R, \{\sigma_{Zk}^N\}), \quad (2.78)$$

where f is a function depending on the model used (e.g., SM5, SM5.4 and SM8), R is the van der Waals radius of a solute molecule. In this approach, the molecular surface tension is constant for the given solvent.

SMD models are widely used in studies involving chemical reactions. Unlike PCM models, it adds G_{CDS} parameter which accounts for the correction of cavitation energy, dispersion energy and structure effects resulting in good estimation of various parameters, such as barrier heights, for solvated systems with strong hydrogen bonding between the solute and the solvent. Moreover, SMD model has the advantage of being parameterised for many solvents, it is applicable to any charged or uncharged solute in any continuum medium [177, 197]. The study presented in this dissertation were solely performed using the SMD model because of the fact that it is the default solvation model in Gaussian 09, the software program utilised throughout the study.

2.3 Geometry optimisation and reaction mechanisms

2.3.1 Geometry optimisation for an isolated system and chemical reaction species involved in reaction mechanism

Geometry optimisation is a procedure that attempts to locate stationary points on a potential-energy surface (PES). Potential energy surface is a mathematical relationship linking the degree (s) of freedom coordinate (s) (e.g., bond length, bond angle or torsion angle) and resultant structural energy [205–209]. A potential energy surface is often represented by diagram illustration, like that shown in Figure 2.4. The drawing considers two degrees of freedom of the internal coordinates (e.g., bond length and torsion angle) versus the resultant energy; this is called an energy profile.

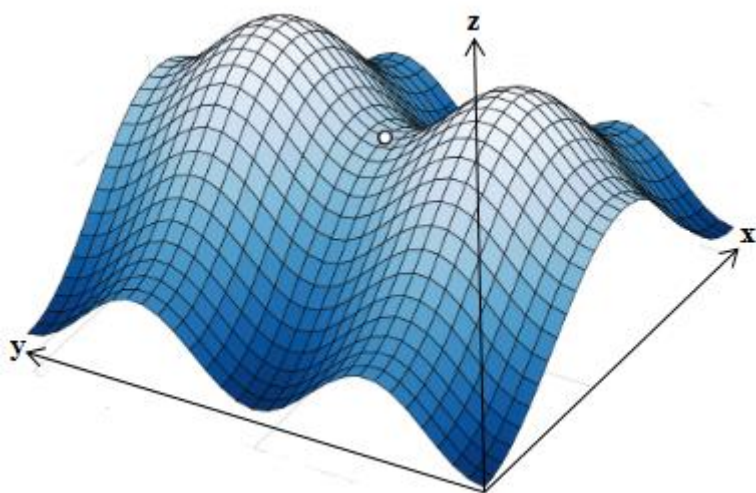


Figure 2.4: An illustration of potential-energy surface diagram showing the relationship between the two degrees of freedom of the internal coordinates; represented as x and y and their resultant energies represented as z [201, 205].

The forces on all the atoms are given by the negative first derivative of the energy with respect to a given coordinate. If a three dimensional surface is considered, then the force

is determined by the negative of the derivative of the energy with respect to the Cartesian coordinates;

$$\mathbf{F} = -\nabla E = -\hat{x} \frac{\partial E}{\partial x} - \hat{y} \frac{\partial E}{\partial y} - \hat{z} \frac{\partial E}{\partial z}. \quad (2.79)$$

The potential energy surface consists of several points on which the force vanishes; in other words, at these points, the first derivative of energy of a molecule with respect to the coordinates of interest is zero. These points are commonly referred to as stationary points. There are three types of stationary points on PES, namely; the minimum, the maximum and the saddle point. A minimum stationary point is the lowest-energy point on a potential-energy surface. There are two types of minima on PES, the global minimum and the local minimum. The global minimum is the lowest-energy minimum on the whole PES while the local minimum is the lowest-energy minimum on some regions of the PES. The three stationary points are differentiated by taking the second derivative of the energy of the molecule with respect to coordinates of interest. A minimum stationary point is a point for which each and every curvature (i.e., second derivative of the energy with respect to a given coordinate) within the Hessian matrix is greater than zero, so that the Hessian matrix is positive definite;

$$\frac{\partial^2 E}{\partial x^2} > 0, \quad \frac{\partial^2 E}{\partial y^2} > 0, \quad \frac{\partial^2 E}{\partial z^2} > 0. \quad (2.80)$$

A maximum point on a potential surface is characterised by the negative second derivative of the energy with respect to any of the coordinates, so that the Hessian matrix is negative definite;

$$\frac{\partial^2 E}{\partial x^2} < 0, \quad \frac{\partial^2 E}{\partial y^2} < 0, \quad \frac{\partial^2 E}{\partial z^2} < 0. \quad (2.81)$$

Saddle point on a potential surface is a point that is characterised by existence of both negative curvatures (i.e., it is a maximum on one side) and positive curvatures (it is a

minimum on all other sides), so that the Hessian matrix is indefinite. The Hessian matrix may contain one or more negative eigenvalue (i.e., second derivative of the energy with respect to the coordinate of interest). If the Hessian matrix contains only one negative eigenvalue, the saddle point found is referred to as the first order saddle point; the negative eigenvalue may be along any of the Cartesian axis; it may be along the x-axis;

$$\frac{\partial^2 E}{\partial x^2} < 0, \quad \frac{\partial^2 E}{\partial y^2} > 0, \quad \frac{\partial^2 E}{\partial z^2} > 0, \quad (2.82)$$

it may be along the y-axis;

$$\frac{\partial^2 E}{\partial x^2} > 0, \quad \frac{\partial^2 E}{\partial y^2} < 0, \quad \frac{\partial^2 E}{\partial z^2} > 0, \quad (2.83)$$

or it may be along the z-axis;

$$\frac{\partial^2 E}{\partial x^2} > 0, \quad \frac{\partial^2 E}{\partial y^2} > 0, \quad \frac{\partial^2 E}{\partial z^2} < 0. \quad (2.84)$$

Similarly, if the Hessian matrix contains two negative eigenvalues, the saddle point found is referred to as the second order saddle point, for instance; the negative eigenvalues may be along the x-axis and y-axis;

$$\frac{\partial^2 E}{\partial x^2} < 0, \quad \frac{\partial^2 E}{\partial y^2} < 0, \quad \frac{\partial^2 E}{\partial z^2} > 0, \quad (2.85)$$

the negative eigenvalues may be along the x-axis and z-axis;

$$\frac{\partial^2 E}{\partial x^2} < 0, \quad \frac{\partial^2 E}{\partial y^2} < 0, \quad \frac{\partial^2 E}{\partial z^2} < 0 \quad (2.86)$$

or the negative eigenvalues may be along the y-axis and z-axis;

$$\frac{\partial^2 E}{\partial x^2} > 0, \quad \frac{\partial^2 E}{\partial y^2} < 0, \quad \frac{\partial^2 E}{\partial z^2} < 0. \quad (2.87)$$

For a chemical system represented by a potential energy surface, a saddle point that has only one negative eigenvalue is known as a transition state structure. In order to study an isolated molecule or features of chemical reactions, it is necessary to be able to locate both minima and the first order saddle points. For an isolated molecule, the minima on PES represent stable conformations. For chemical reactions, the minima on the PES represent reactant, intermediate and products species; first-order saddle points on a PES describe transition state structures. When reaction species (i.e., reactants, transition states, intermediates and product species) have to be determined, the optimisation procedure has to follow a proposed reaction path. A reaction path is the path through which optimisation proceeds to connect the reactant and product species in the proposed reaction mechanism, stepping through all possible intermediates and transition states connecting the reactant species and product species. There may be several possible reaction paths for a given reaction. The reaction path corresponding to the minimum Gibbs free energy is called the minimum energy path (MEP).

Negative eigenvalue of a stationary point can be determined by using the vibrational analysis technique [209–213], which requires mass weighting of the Hessian matrix. The negative eigenvalue of the Hessian matrix represents an imaginary vibration in a generalised harmonic vibrational problem [209].

The procedure for geometry optimisation, to obtain either minima or first order saddle points on a potential energy surface, requires a reasonable starting input structure and selection of appropriate coordinate system. A good input structure increases accuracy in optimisation and utilises minimal computational time due to reduced optimisation cycles. The input structure has to be created in such a way that it corresponds to the nearest point to the local minimum (when searching for the reactants, intermediate and product species) or a saddle point (when searching for a transition state) on PES. This requires good

knowledge on the nature of the starting reactant structure or transition state to be able to use chemical intuition to model its input close to the desired structure.

The choice of coordinate system (ξ) also plays an important role in the effectiveness of optimisation because it determines the structure of the Hessian matrix. It may depend on the type of a molecule, size of a molecule and the reaction being studied. Geometry coordinate systems that are commonly used include the Cartesian coordinate system and the internal coordinate system [210, 211]. The Cartesian coordinate system is a system specifying a point at an intersection of three (or two) fixed axes forming the right angle with respect to the origin. It uses direct approach to specify the location of atoms in a molecule; For instance, a system with N atoms or nuclei has $3N$ Cartesian coordinates in space. The three variables used (i.e., x , y and z for a non-spherical system or r , θ and ϕ for a spherical system) describes the position in space of an atomic nucleus or basis function [210]. An example of hydrogen peroxide consisting of Cartesian coordinates is as follows;

O	2.26351960	0.99450098	-4.08080076
H	3.22351960	0.99450098	-4.08080076
O	1.82289455	2.23878774	-4.08080076
H	0.86289615	2.23878831	-4.08255548

where the first column represents the atomic symbols, the second, the third and fourth columns represent the x , y and z coordinates. Although the Cartesian coordinate system is simple and straight forward, it is highly coupled resulting in poor optimisation.

The internal coordinate system is a system in which a reaction corresponding to PES does not depend on the absolute position (x , y and z or $\mathbf{r}$, θ and ϕ) of the reaction, but rather depends only on the relative positions of a molecule, which can be expressed as bond length, bond angle and torsion angle [210, 214]. In this approach, the translation and the rotation motions of the entire system are neglected. It is based on the fact that when considering a non-linear system, each motion consist of 3 degrees of freedom (i.e., bond

length, bond angle and torsion angle), therefore, for the two motions; six degrees of freedom are being neglected. In this way, the dimensionality of a PES has a form;

$$3N - 6, \quad (2.88)$$

and for a linear system (five degrees of freedom are neglected), the dimensionality of PES has an expression;

$$3N - 5. \quad (2.89)$$

The internal coordinate system has considerable advantages over Cartesian coordinate system such as; it is less coupled, which makes it easy to approximate solutions for the Hessian matrix. The disadvantages of this system is that when considering a system with more than two atoms; the number of the internal coordinates becomes more than the number of the degrees of freedom resulting in what is known as redundant problem [137, 139, 140].

The Z-matrix approach is utilised to give full description of large molecular system with the use of internal coordinates. It is available in many popular programmes including Gaussian [215]. Consider the following hydrogen peroxide Z matrix coordinate set up;

```
H
O  1  0.9
O  2  1.4  1  105.0
H  3  0.9  2  105.0  1  120.0
```

The first line of the matrix consists of the first atom for the matrix, which is the hydrogen (H1) atom found at the intersection between the first column from the left and the first row from above. The second line of the matrix consists of the second atom for the matrix, which is the oxygen atom (O2) atom found at the intersection between the first column from the left and the second row from above; the second line also consists of the bond length value between H1 and O2, which is 0.9 Å. The third line of the matrix consist of

the third atom for the matrix, which is another oxygen atom (O3) found at the intersection between the first column from the left and the third row from above; the third line consists of the bond length of a value of 1.4 Å (between O2 and O3 atoms) and a bond angle of a value of 105.0° (between H1, O2 and O3 atoms). The fourth line of the matrix consists of the fourth atom for the matrix, which is another oxygen atom (H4) found at the intersection between the first column from the left and the fourth row from above; the fourth line consists of the bond length of a value of 0.9 Å (between O3 and H4 atoms), a bond angle of a value of 105.0° (between H1, O2 and O3 atoms) and a torsion angle of 120.0° (formed by H1, O2, O3 and H4 atoms).

2.3.2 Optimisation algorithms for locating minima and transition state structures during the optimisation procedure

Several optimisation algorithms have been developed for locating the minima and first order saddle point structures on a potential energy surfaces [216–222]; they include the Nelder-Mead simplex method [217], the conjugate gradients method [216], the Newton-Raphson method [211, 218–222] and synchronous transit methods [211]. The most widely utilised optimisation algorithm approach in most quantum mechanical softwares is the Newton-Raphson method for both location of minima and first order saddle points and the synchronous transit methods for location of first order saddle points. Both methods are hereby discussed in brief.

Newton-Raphson method considers the potential energy surface of a given molecular system as a Taylor series of the form [216];

$$E_1 = E_0 + g_0 (x_1 - x_0) + \frac{1}{2} H_0 (x_1 - x_0)^2, \quad (2.90)$$

where g_0 is the first derivative of energy with respect to the coordinate of interest (x_0) and H_0 is the starting approximate Hessian matrix for the required input structure; we can let $x_1 - x_0$ be ξ , the expression can be rewritten as;

$$E_1 = E_0 + g_0 \xi + \frac{1}{2} H \xi^2. \quad (2.91)$$

In order to utilise the Newton-Raphson method, it is necessary that the new point is obtained by moving to the minimum of the potential energy surface. This is achievable by determining the derivative of the energy function E for the quadratic energy expression with respect to ξ , and setting it to zero [216, 223] ;

$$\frac{dE_1}{d\xi} = \frac{dE_0}{d\xi} + g_0 \frac{d\xi}{d\xi} + \frac{1}{2} H \frac{d}{d\xi} \xi^2 = 0. \quad (2.92)$$

Since E_0 is independent of ξ , the first term on the right becomes zero and the overall expression becomes;

$$g_0 + H\xi = 0, \quad (2.93)$$

which simplifies to;

$$\xi = -g_0 H_0^{-1}. \quad (2.94)$$

Since $\xi = x_1 - x_0$, we can further determine that the value of x_1 is given as;

$$x_1 = x_0 - g_0 H_0^{-1}. \quad (2.95)$$

The process of obtaining the x_1 term is referred to as the Newton step. The step could be repeated (iterated) several times to obtain for instance $x_2, x_3, \dots x_i$ terms, however, the gradient will not be exactly zero (for each step) because the potential energy surface for molecular systems is not exactly quadratic [211]. In order to obtain a zero gradient, the iterative procedure should be repeated by solving the following system of linear equations to obtain the Newton-Raphson (also known as quasi-Newton) method for optimisation;

$$H_k \xi = -g_k. \quad (2.96)$$

Newton-Raphson approach expressed in equation 2.96 consists of an improved Hessian matrix (H_k), which is improved through an updating procedure during the course of the optimisation. The update procedure on the Hessian should consider that the Hessian matrix should always be definite positive for optimisation towards a minimum structure and it should contain one negative eigenvalue for optimisation that proceeds towards the first order saddle point. For this reason, different suitable Hessian matrix update methods have been developed towards optimisations that leads to a minimum and towards optimisations that lead to a first order saddle point [223]. The most widely utilised Hessian matrix update approach is the Broyden-Fletcher-Goldfarb-Shanno minimization (BFGS) method [224];

$$H_k = H_{k-1} + \Delta H_k^{\text{BFGS}}, \quad (2.97)$$

$$\text{where } \Delta H_k^{\text{BFGS}} = - \left(\frac{\Delta g_k \Delta g_k^T}{\xi_{k-1}^T \Delta g_k} + \frac{H_{k-1} \xi_{k-1} (H_{k-1} \xi_{k-1})^T}{\xi_{k-1}^T H_{k-1} \xi_{k-1}} \right) \quad \text{and } \Delta g_k = g_k - g_{k-1}.$$

BFGS updates converge to a meaningful value only if accurate line searches are used during the optimisation. An algorithm is a line search method (shown in Figure 2.5); it seeks the minimum of a defined nonlinear function by selecting a reasonable direction vector that, when computed iteratively with a reasonable step size, will provide a function value closer to the absolute minimum of the function [216, 223]. However, standard optimisations do not always meet this criterion and as a consequence, a regular restart of the update may be necessary. An alternative approach to BFGS is to use the symmetric rank one (SR1) update (also referred to as the Murtagh-Sargent update) approach, which converges without requirement for exact line searches [225];

$$H_k = H_{k-1} + \Delta H_k^{\text{SR1}}, \quad (2.98)$$

$$\text{where } \Delta H_k^{\text{SR1}} = \left(\frac{(\Delta g_k + H_{k-1} \xi_{k-1})(\Delta g_k + H_{k-1} \xi_{k-1})}{(\Delta g_k + H_{k-1} \xi_{k-1})^T} \right).$$

For first order saddle point, the selected update should not force the Hessian matrix to be positive definite. The SR1 update may be utilised for this objective as well as the Powell-symmetric-Broyden (PSB) update approach [223, 225];

$$\mathbf{H}_k = \mathbf{H}_{k-1} + \Delta \mathbf{H}_k^{\text{PSB}}, \quad (2.99)$$

$$\text{where } \Delta \mathbf{H}_k^{\text{PSB}} = (\Delta \mathbf{g}_k + \mathbf{H}_{k-1} \xi_{k-1})^T \xi_{k-1} \frac{\xi_{k-1}^T \xi_{k-1}}{(\xi_{k-1}^T \xi_{k-1})^2} - \frac{(\Delta \mathbf{g}_k + \mathbf{H}_{k-1} \xi_{k-1}) \xi_{k-1}^T + \xi_{k-1} (\Delta \mathbf{g}_k + \mathbf{H}_{k-1} \xi_{k-1})^T}{\xi_{k-1}^T \xi_{k-1}}.$$

In summary, the overall procedure for optimisation (Figure 2.5), including both the Newton-Raphson and the necessary updates on the Hessian matrix involves providing an input structure from which an initial matrix can be generated. The energy and the gradient for the initial geometry are then calculated followed by checking of convergence on gradient and displacements. If the convergence criteria are met, then the optimisation is considered successful. However, if the convergence criteria are not satisfied, an update on the Hessian matrix is necessary and any of the update method can be selected for this task, taking into consideration to which stationary point one intends to reach; for instance, if the desired stationary point is the minimum, then the BFGS update method could be selected. If the BFGS fails, the other update methods (which does not require line search) are used followed by repeating the optimisation procedure from the determination of energy and gradient to obtaining the geometry until a successful optimisation is obtained.

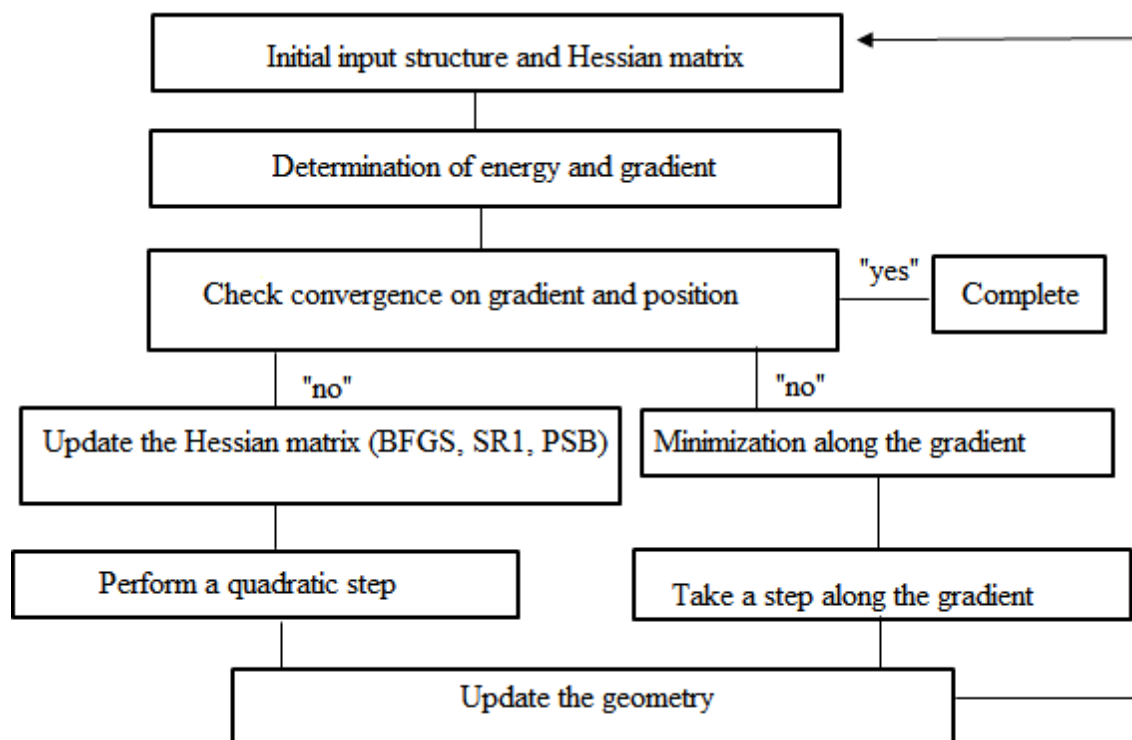


Figure 2.5: Schematic diagram showing the optimisation procedure steps for the location of minima and first order saddle points on PES [201, 205].

The attempt to locate the first order saddle point is however sometimes much more complex than the location of the minimum point on the potential energy surface, mainly because in such optimisations, the selected algorithm has to follow the directions where a saddle point is a minimum (the Hessian matrix must be positive in all directions) and also the direction in which the saddle point is a maximum (the Hessian matrix must be negative in one direction) on PES. Therefore, several techniques have been developed specifically for the location of the transition state structures, among which is the synchronous transit methods (which include linear synchronous transit method and quadratic synchronous transit method). It is an approach that uses the optimised geometries of the reactant and the product species to locate of the transition state. It uses

either linear synchronous transit (LST) or quadratic synchronous transit (QST) approach to get closer to the quadratic region close to the transition state.

Linear synchronous transit method describes an approach which interpolates a reaction pathway in order to connect the reactant and product species (whose geometries are known and which correspond to minimum points on PES), thereby identifying a set of structures that lie between the reactants and product species. The reaction pathway obtained in this way is referred to as the transit path and the structure that occurs at the maximum energy along the transit path (between two minimum points; the reactant and product species) is a first guess to a saddle point. However, because of its nature, LST approach does not usually follow the minimum energy path and the saddle point obtained, corresponding to the maximum energy along the reaction path, may have more than one eigenvalue. Therefore, there is a need to refine the findings of LST method by introducing the QST approach.

The QST method interpolates a reaction pathway that is parabolic in nature to connect the reactant and product species. It searches for a maximum point along the quadratic curve linking the reactant and the product and a minimum in all other directions that are perpendicular to the parabolic curve [208–212]. In a similar manner to LST, the maximum point on the quadratic transit path corresponds to a first guess to a saddle point. Once the saddle point corresponding to one negative eigenvalue is found, the quasi-Newton method may be initiated to complete the optimisation. If the saddle point with one negative eigenvalue is not found, using the QST approach, the QST2 and QST3 approaches may be utilised. In the QST2 approach, one reactant structure (on the reactants side) and one product structure (on the products side) are utilised to approximate a quadratic transit path in order to generate the guess transition state; in the QST3 approach, three structures are selected and connected by a quadratic path [201, 211]. The third structure should resemble the expected transition state and it may be among the reactants. A series of steps may then be taken along the quadratic path until a maximum point is obtained along the path. The Quasi-Newton approach may then be initiated from the found maximum point on the path to complete the optimisation. The algorithms that combine synchronous transit method and quasi-Newton method are referred to as synchronous transit-guided quasi-Newton (STQN) method [201].

2.3.2.3 Intrinsic reaction coordinate

The intrinsic reaction coordinate (IRC) approach is a method utilised to follow the reaction path with an objective of confirming that the reactant and product species are linked by the transition state found for the particular reaction. It is defined as a minimum energy reaction pathway (i.e., it follows the steepest descent path) on PES in mass-weighted Cartesian coordinates (x) from the transition structure [226–228] towards either the reactant or the product species. IRC is a solution to the following equation;

$$v(s) = \frac{dx(s)}{ds}, \quad (2.100)$$

where s is a coordinate along the IRC path and v is a normalised tangent vector of IRC evaluated at the point on a curve. The tangent vector corresponds to the negative eigenvector obtained for the transition state through the PES scan, where the coordinate along the IRC is zero. At all other points where $s < 0$;

$$v = \frac{-g}{|g|}, \quad (2.101)$$

and for a case where $s > 0$, we get ;
$$v = \frac{g}{|g|}. \quad (2.102)$$

The mass-weighted gradient vector (g) in equation 2.101 and equation 2.102 have to be repeated numerically until $s = 0$. This is because IRC has been defined to be a path that the molecule takes by moving down the product and reactant valleys with zero kinetic energy [226, 228]. In this way, IRC-following algorithms are proposed in order to reduce the number of gradient vector calculations. Optimisation of a correct high energy structure on PES to finding a transition state of interest is very important in this approach because IRC confirms if indeed the product and the reactant species are joined by the transition state obtained for the reaction. The IRC following algorithm is available in the Gaussian program; it can be accessed using the keyword **irc**.

2.4 Radical scavenging reaction mechanisms of antioxidants

A molecule's antioxidant effect within a biological system may be exerted through four main mechanisms, the hydrogen atom transfer (HAT) pathway, the single electron transfer (SET) pathway, single electron transfer-proton transfer (SET-PT) pathway and sequential proton-loss electron-transfer (SPLET) pathway. Although, most of the antioxidant molecules may be capable of effecting the different types of mechanisms [229], the HAT and SET mechanisms are often the major contributors to the overall phenolic antioxidant activity while SET-PT and SPLET are often considered to have minor contributions towards antioxidant activity of phenolic derivatives [46, 230, 231].

The HAT mechanism is assessed through the ability of the antioxidant molecule to donate its phenolic hydrogen atom. The ability of the antioxidant molecule to donate its phenolic hydrogen atom towards the radical species is measured through the H–O bond dissociation enthalpy (*BDE*). Let us assume for instance that the phenolic molecule of interest is denoted as ArOH. Let us also assume that this phenolic molecule interacts with $\bullet\text{OOH}$, and in the process donates its phenolic H atom to $\bullet\text{OOH}$ in order to form a phenoxyl radical and hydrogen peroxide, through the equation;



In order to estimate the *BDE* for this type of a reaction, the enthalpy energies of the product species is added together; the enthalpy energies of the reactants species is also separately added together. Then the *BDE* value for the O–H bond is considered as the sum of the enthalpies of the product species minus the sum of the enthalpies of the reactant species;

$$\Delta H_{BDE} = H(\text{ArO}\bullet) + H(\text{H}_2\text{O}_2) - H(\bullet\text{OOH}) - H(\text{ArOH}). \quad (2.104)$$

The SET-PT mechanism for radical scavenging proceeds through two steps; the first step involves the transfer of an electron from ArOH to $\bullet\text{OOH}$, forming a cationic radical species and anionic species;



The amount of energy required for this chemical process is measured through the adiabatic ionisation potential (*IP*) thermodynamic parameter, which is estimated through the equation;

$$\Delta H_{IP} = H(\text{ArOH}\bullet^+) + H(\text{OOH}^-) - H(\bullet\text{OOH}) - H(\text{ArOH}). \quad (2.106)$$

The subsequent step involves transfer of the proton from $\text{ArOH}\bullet^+$ to the anion;



The amount of energy required for this chemical process is measured using the proton dissociation enthalpy (*PDE*), which for this equation is estimated as;

$$\Delta H_{PDE} = H(\text{ArO}\bullet) + H(\text{H}_2\text{O}_2) - H(\text{ArOH}\bullet^+) - H(\text{OOH}^-). \quad (2.108)$$

The sequential proton-loss electron-transfer (SPLET) also proceeds through two steps; in the first step, it is assumed that some of the molecules of ArOH react within a basic medium to form anionic species;



The thermodynamic parameter describing this step is the proton affinity (*PA*), it is calculated using the equation as;

$$\Delta H_{PA} = H(\text{ArO}^-) + H(\text{H}_2\text{O}_2) - H(\text{ArOH}) - H(\text{OOH}^-). \quad (2.110)$$

The second step is the interaction of the anionic form of the antioxidant species with the radical species, resulting in the formation of the phenoxyl radical;



The thermodynamic parameter relevant for this reaction is the electron transfer enthalpy (*ETE*), which is estimated through the equation;

$$\Delta H_{ETE} = H(\text{ArO}^\bullet) + H(\text{OOH}^-) - H(\text{ArO}^-) - H(\bullet\text{OOH}). \quad (2.112)$$

A comparison of the *BDE*, *IP*, *PDE*, *PA* and *ETE* thermodynamic parameters gives information on the most thermodynamically preferred reaction mechanism. Therefore, for this reason, all the four mechanisms have been included in the investigation for the phloroglucinol molecules chosen for study in this dissertation.

2.5 Estimation of reaction rate constants

2.5.1 Reaction rate constants in gaseous phase

Chemical reactions may take place through a single step mechanism or a multistep mechanisms. A single step mechanism involves only the reactant species, transition state and product species. If we consider A and B to be reactant species and P as product, then we can write;



where A and B denote the isolated reactant species and P represent the product species. A multistep reaction mechanism involves the reactant species, transition state, intermediate(s) and product species;



where I is the intermediate. Reaction rate is a measure of change in concentration of the involved species per unit time. Often, it is expressed as a differential of the concentration of the reactant species with respect to time, in which case the rate represents a decrease in the concentration of the reactant species with time. In a simplest case of a reaction;



the rate of the reaction is expressed as;

$$\text{rate} = -\frac{d[A]}{dt}, \quad (2.116)$$

where $[A]$ is the concentration for the reactants. However, the rate of the reaction is also proportional to the concentration of the reactant species present;

$$\text{rate} \propto [A]. \quad (2.117)$$

where $\propto$ represents the proportionality between the rate and the concentration of the reactant A per unit time. In order to replace the proportionality with an equal sign, we have to introduce the coefficient k , known as rate constant. In this way, the rate is expressed as;

$$\text{rate} = k[A]. \quad (2.118)$$

Equating equation (2.116) with (2.118), we can write;

$$\frac{d[A]}{dt} = k[A]. \quad (2.119)$$

We can rearrange this equation and integrate it to obtain the rate constant;

$$\frac{d[A]}{[A]} = kdt. \quad (2.120)$$

Consider that at time zero (t_0) the concentration of the reactant is $[A]_0$ and at any other selected time (t), the remaining concentration of the reactant is $[A]_t$ and integrate within the limits, we obtain;

$$\int_{[A]_0}^{[A]_t} \frac{d[A]}{[A]} = k \int_{t_0}^t dt, \quad (2.121)$$

$$\ln[A] \Big|_{[A]_0}^{[A]_t} = kt \Big|_{t_0}^t. \quad (2.122)$$

Applying the limits of integration gives;

$$\ln \frac{[A]_t}{[A]_0} = kt. \quad (2.123)$$

So that at any other time, the concentration of the reactant is found as;

$$[A]_t = [A]_0 e^{kt} \quad (2.124)$$

Therefore, the concentration of the reactant at any time is determined by the rate constant k . A high value of the rate constant implies that the reaction will be fast.

Rate constants are determined from optimised species (and their energies) of a reaction (obtained in section 2.3.3). There are several theories developed for calculation of the reaction rate, two of which are the collision theory and the transition state theory. Collision theory states that for a chemical reaction to take place, molecules must collide. Not all colliding molecules do react but molecules undergoing effective collision form a reaction. For a collision to be effective, it must meet the following requirements;

- collision must occur between the correct molecules,
- molecules must be sufficiently energetic in order to disrupt relevant bonds within reactant molecules and
- molecules must have proper orientation to interact together.

The transition state theory (TST) explains the formation of chemical reactions through the concept of activated complex, which corresponds to a transition state structure. TST states that a reaction can occur if and only if the reactant species have enough energy to

overcome the energy barrier (activation energy). Figure 2.6 shows a schematic representation of a chemical reaction pathway connecting the reactant, transition state and product species, as suggested within the TST. The activation energy is then estimated as the energy difference between the energy of the transition state (TS) and the energy of the reactant species (A + B).

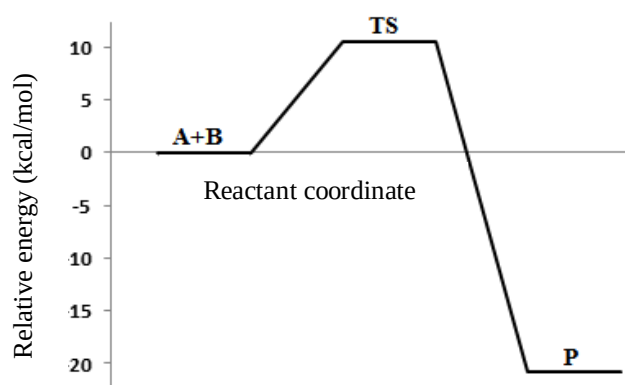


Figure 2.6: A schematic diagram showing a single step chemical reaction taking place between reactants (A and B). The energies of the transition states (TS) and product complex are calculated with respect to the energy of the reactant molecules

Beside concentration, another factor that contribute to the rate of the reaction is the temperature. At a higher temperature, molecules have high kinetic energy which results in effective collision of molecules. Rate constant k of a reaction increases with an increasing temperature. The relationship between rate constant and temperature can be expressed through either the Arrhenius equation or the Eyring equation.

Arrhenius equation. Arrhenius equation is an equation used show the effect of temperature on the rate constant;

$$\ln k = \ln (A) - \frac{E_a}{RT}, \quad (2.125)$$

or in an exponential form as;

$$k = A e^{-\frac{E_a}{RT}}, \quad (2.126)$$

where k is the rate constant, A , is the factor related to the frequency of the collisions, E_a is the activation energy of the reaction, R is the gas constant and T is the absolute temperature.

The Eyring equation is used in the study of solution reactions and mixed phase reactions; it is also based on transition state theory. The transition state theory has two assumptions of which the first one states that equilibrium exists between the reactants and the activated complex and secondly it states that the reaction coordinate describing decomposition of the activated complex can be mapped on to a single energetic degree of freedom of the activated complex [7, 68]. Eyring equation is expressed as;

$$k_{\text{act}} = \frac{k_B T}{h} \exp\left(\frac{-\Delta G^\ddagger}{RT}\right), \quad (2.127)$$

where h is the Planck's constant and k_B is the Boltzmann's constant, $\Delta G^\ddagger$ is the activation Gibbs free energy; it is estimated as the energy difference between the transition state structure (TS) and the reactant complex (RC). The Gibbs free energy values utilised to calculate the rate constant are those that include the zero-point energy correction.

In multistep reactions, other approximation approaches have to be introduced in order to obtain the overall reaction rate constant. The often utilised approximations include the steady state approximation and the pre-equilibrium approximations. Steady state approximation assumes that the change in the concentration of the intermediate with respect to time in all the steps of the reaction is equal to zero. This assumption stems from the consideration that a reactive intermediate (IM) is used up as soon as it is formed, so its concentration will remain low and constant throughout the reaction time. In other words, the steady state approximation works only for multistep reactions in which there are no possibility of the existence of the equilibrium between the intermediate and the reactant species. On the other hand, the pre-equilibrium approximation estimates the rate constants of the reactions by assuming that in a multistep reaction, the reactant species

and the intermediate reach equilibrium [140, 151] and that the intermediate may quickly decay to form the product. To illustrate what this means, consider a multistep reaction consisting of the first step being a bimolecular reaction and the second step being a unimolecular reaction, the overall reaction can be written as;



The first step of the reaction proceeds forward to form IM at a rate constant k_1 , so that the rate for the formation of the intermediate can be expressed as;

$$\frac{d[IM]}{dt} = k_1[A][B]. \quad (2.129)$$

The intermediate may decay to form reactant molecules through reverse reaction at a rate constant k_2 , the corresponding reaction rate can be written as;

$$\frac{d[IM]}{dt} = -k_2[IM]. \quad (2.130)$$

If we equate equation 2.129 and 2.130 and solve for the concentration of the intermediate species, we get;

$$k_1[A][B] = -k_2[IM]. \quad (2.131)$$

From which we can write;

$$\frac{[IM]}{[A][B]} = -\frac{k_1}{k_2}. \quad (2.132)$$

At equilibrium the ratio of the product of the concentrations of the product species with the product of the concentration of the reactant species equal to the equilibrium constant k_c , with each concentration of the species involved raised to the respective stoichiometric

number. If we consider a simplified case in which all the stoichiometric numbers in equation 2.131 are equal to unit, then equation 2.132 can be written as;

$$\frac{[\text{IM}]}{[\text{A}][\text{B}]} = -\frac{k_1}{k_2} = k_c. \quad (2.133)$$

This equation can be rearranged so that the concentration of the intermediate can be written in terms of the concentration of the reactants and the equilibrium constant (k_c);

$$[\text{IM}] = k_c [\text{A}][\text{B}]. \quad (2.134)$$

The product complex P may form from IM at the rate constant k_3 , through the forward reaction. The equilibrium is assumed to be established before the product complex is completely formed [140, 151]. Assuming that $k_2 \gg k_3$, the rate of product formation can be expressed as;

$$\frac{d[\text{P}]}{dt} = k_3 [\text{IM}]. \quad (2.135)$$

Substituting equation 2.134 into equation 2.135 gives the rate of product formation;

$$\frac{d[\text{P}]}{dt} = k_3 k_c [\text{A}][\text{B}]. \quad (2.136)$$

If we assume the overall rate constant due to activation, starting from reactants to products, to be k_{act} then we can write

$$k_{\text{act (overall)}} = k_3 k_c. \quad (2.137)$$

Therefore, estimation of the overall rate constant requires obtaining values for k_1 , k_2 and k_3 . The k_1 and k_3 values are estimated by utilising equation 2.137. k_2 is found by using the condition that at equilibrium, the Gibbs free energy at standard condition (ΔG°) is equal to the product of RT and the natural logarithm of equilibrium constant, k_c ;

$$\Delta G^\circ = -RT \ln k_c, \quad (2.138)$$

where R is the gas constant and T is the standard absolute temperature.

2.5.2 Reaction rate in solution: inclusion of molecular diffusion effects

The rate constant for the reaction occurring in condensed phase (in solution) is different from the rate constant for the reaction in gaseous phase (*in vacuum*). The difference is in the fact that the estimation approach for the rate constant of the reaction in solution takes in account that the solute molecule diffuse in the presence of the solvent molecules. Molecular diffusion is defined as the transfer or the movement of particles from the region of high concentration (in gaseous phase) to a region of low concentration (in a solvent) in a random motion. Each solute molecule in a reaction is surrounded by the solvent molecules in which when the two molecules are in the same solvent shell, are said to encounter (interact with) each other; the resultant product is called the encounter pair. For simplicity sake, consider a reaction consisting of solute A and solute B interacting in the presence of the solvent to form the encounter pair (AB) at a diffusion rate constant k_D ;



With an assumption that the all the stoichiometric numbers in equation 2.139 are equal to a unit, the reaction is a first order reaction and its rate of product formation has a mathematical formula;

$$\frac{d[AB]}{dt} = k_D[A][B]. \quad (2.140)$$

In turn, the same process of diffusion, (which brought A and B into forming an encounter pair) may also separate solute A and solute B, resulting in a non-reactive encounter; in such a case, AB may undergo reversible reaction to form isolated A and B molecules at a rate constant k_r ;



The rate constant for the reversible reaction is also a first order reaction, with a mathematical form;

$$\frac{d[AB]}{dt} = -k_r[AB]. \quad (2.142)$$

If the intermediate AB accumulate enough energy, it may proceed forward to form product (P) at a rate constant k_f ;



The rate of formation of the product is also a first order reaction, with the mathematical form;

$$\frac{d[AB]}{dt} = -k_f[AB]. \quad (2.144)$$

From equation 2.139, 2.141 and 2.143 the overall reaction in solution can be written as;



where AB is the intermediate and the rate constant for the overall reaction is obtained from equation 2.140, 2.142 and 2.143, with an overall mathematical form of

$$\frac{d[AB]}{dt} = k_D[A][B] - k_r[AB] - k_f[AB]. \quad (2.146)$$

When using the steady state approximation, to set the rate of the concentration of the intermediate with respect to time equal to zero, equation 2.146 becomes;

$$k_D[A][B] - k_r[AB] - k_f[AB] = 0. \quad (2.147)$$

When solving equation 2.147, it is found that the concentration of the intermediate [AB] has a form;

$$[AB] = \frac{k_D[A][B]}{k_f + k_r}. \quad (2.148)$$

The rate of product formation is expressed as;

$$\frac{d[P]}{dt} = k_f[AB]. \quad (2.149)$$

Substituting equation 2.148 into equation 2.149, we obtain;

$$\frac{d[P]}{dt} = \frac{k_D k_f [A][B]}{k_f + k_r}, \text{ which can be written as } \frac{d[P]}{dt} = k_{app} [A][B], \quad (2.150)$$

$$\text{where } k_{app} = \frac{k_D k_f}{k_f + k_r}, \text{ represent the apparent rate constant.} \quad (2.151)$$

In this equation k_D , has the form [140, 151];

$$k_D = 4\pi R_{AB} D_{AB} N_A, \quad (2.152)$$

where A and B denote molecules that have radius R_A and R_B respectively in solution N_A is Avogadro's constant, R_{AB} is the reaction distance. If A and B are considered to have a spherical shape, then R_{AB} is the distance at which A and B contact each other, so that they can react; they interact when $R_{AB} = R_A + R_B$. D_{AB} is obtained as the sum of D_A and D_B , where D_A and D_B are the individual diffusion coefficients of reactant A and

reactant B respectively. The individual diffusion coefficients are obtained from Stokes-Einstein equation [10, 232–234]; in this way, the diffusion coefficient of A and B are given by the expressions;

$$D_A = \frac{k_B T}{6\pi\eta R_A} \quad \text{and} \quad D_B = \frac{k_B T}{6\pi\eta R_B}. \quad (2.153)$$

where η is the viscosity of the solvent in which the reaction is performed.

2.6 Quantum theory of atoms in molecules

Quantum Theory of Atoms in Molecules (QTAIM) analysis [235] is an approach used to characterise the bonding properties within an isolated molecule as well as reaction species, in terms of their electron density distribution as well as the electron density energy. The topology of the electron density (ρ) is controlled by the attractive forces between the two nuclei in a molecule. The word “critical point” is often used in QTAIM, which is defined as a point in space where the first derivative of electron density ($\nabla\rho$) with respect to nuclear position is zero [236];

$$\nabla\rho = i\frac{d\rho}{dx} + j\frac{d\rho}{dy} + k\frac{d\rho}{dz}, \quad (1.154)$$

where i , j and k are vectors, $\nabla\rho = 0$ at the critical point and at infinity but it is not zero at all other points. The different types of critical points include the minimum, the maximum and the saddle point. The minimum, maximum and the saddle point are differentiated using the second derivative of the electron density ($\nabla^2\rho$) with respect to the position of interest. The curvatures at the critical points are obtained by solving a Hessian matrix; which consist of nine curvatures elements. It has a mathematical form [237];

$$\rho(\mathbf{r}) = \begin{pmatrix} \frac{\partial^2 \rho}{\partial x^2} & \frac{\partial^2 \rho}{\partial x \partial y} & \frac{\partial^2 \rho}{\partial x \partial z} \\ \frac{\partial^2 \rho}{\partial y \partial x} & \frac{\partial^2 \rho}{\partial y^2} & \frac{\partial^2 \rho}{\partial y \partial z} \\ \frac{\partial^2 \rho}{\partial z \partial x} & \frac{\partial^2 \rho}{\partial z \partial y} & \frac{\partial^2 \rho}{\partial z^2} \end{pmatrix}, \quad (2.155)$$

where ρ depends on position $\mathbf{r}$ at critical point between the two nuclei. The second derivative is positive throughout for the minimum, negative throughout for the maximum and possess one negative curvature for the first order saddle point. When equation 2.155 is solved diagonally with the help of the unitary transformation matrix (which introduces principal axes x' , y' and z' to the Hessian matrix [238, 239]). The resultant eigenvalues obtained as a result of solving the second derivative of energy with respect to principal axis are λ_1 , λ_2 and λ_3 ;

$$\nabla^2 \rho(\mathbf{r}) = \underbrace{\frac{\partial^2 \rho(\mathbf{r})}{\partial x'^2}}_{\lambda_1} + \underbrace{\frac{\partial^2 \rho(\mathbf{r})}{\partial y'^2}}_{\lambda_2} + \underbrace{\frac{\partial^2 \rho(\mathbf{r})}{\partial z'^2}}_{\lambda_3}. \quad (2.156)$$

Critical points are classified differently based on the rank (ω) and its corresponding signature (σ). The rank is defined as the number of non-zero eigenvalues (which is the non-zero solutions obtained from solving the curvatures in the Hessian matrix); which in this case is $\omega = 3$. The signature represents the algebraic sum of the signs of the eigenvalues. There are four possible types of the non-zero eigenvalues for critical points; these are [236–239];

- $(3, -3)$; all the three curvatures are negative and ρ is a local maximum
- $(3, -1)$; two curvatures are negative and ρ is a maximum in their corresponding plane. However, along the third axis, which is perpendicular to the plane, it is a minimum
- $(3, +1)$; two curvatures are negative and ρ is a minimum in their corresponding plane. However, along the third axis, which is perpendicular to the plane, it is a maximum

- (3, +3); all the three curvatures are positive and ρ is a local minimum

All the types of critical points correspond to the types of elements of chemical bonds. (3, -3) is a nuclear critical point, meaning that the electron distribution occurs at the nuclear position; (3, -1) corresponds to the bond critical point (BCP) – where the electron density is found between the two nuclei connected by a chemical bond; (3, +1) corresponds to a ring critical point (RCP) – where chemical bonds are connected to form a ring. Moreover, the BCP and the RCP properties define molecular graphs, which bounds a chemical bond and a ring surface respectively. For a critical point (3, +3); the chemical element obtained is a cage critical point; where the bond paths enclose the interior of the molecule with ring surfaces. The molecular graphs (representing molecular structures) may provide information on the presence of any intermolecular interactions between the two reactant molecules within the reactant complex or between the product molecules within the product complex; BCP data play an important role in elucidating the properties of the reaction species. Within the atoms in molecules (AIM) analysis scheme, any two intramolecular or intermolecular bonded atoms are connected by a bond paths. The bond path represents the gradient paths of the electron density starting at the critical point (where the gradient of the electron density is zero) and terminating at the two nuclei of the atoms. The magnitude of the electron density (ρ) at a given bond critical point is related to the bond strength while the Laplacian of the electron density ($\nabla^2\rho$) provide information on the bond order [240–243].

Other important bond critical point data include the kinetic (G) and potential (V) electron energy densities, which together constitute the overall electron energy density (H); the relationships between the electron energies and $\nabla^2\rho$ can be described using the two following equations;

$$\frac{1}{4}\nabla^2\rho(r) = 2G(r) + V(r) \text{ and} \quad (2.157)$$

$$H(r) = V(r) + G(r), \quad (2.158)$$

where r is the position of electron density at the BCP. For the strongest bonds, (such as covalent bonds), $V < 0$ and relatively large, $G > 0$, $H < 0$ and $\nabla^2\rho < 0$. In such systems, the shared electrons are localised in the inter-nuclear space between the atoms of interest [243]. The large value of V at the BCP can be explained by the fact that within the inter-nuclear region, electrons are relatively energetically stable. Weak bonds, such as H-bonding interactions, are described by $H > 0$ that is close to zero, $G > 0$, $V < 0$ and $\nabla^2\rho > 0$. However, the positive value of G predominates over the negative value of V , since the electrons are energetically less stable in the region between two closed-shell systems [243].

2.7 The Gaussian calculation and visualisation programs

The Gaussian program is a computational chemistry software that is used to calculate various atomic and molecular properties. It has been updated continuously since its development in order to improve its efficiency. Its latest version is **Gaussian16** [244]. The Gaussian program is capable of performing different types of calculations for electronic structure modelling including optimisation of isolated molecules as well as complex molecules, determination of molecular properties such as thermodynamic properties (e.g., enthalpy, entropy and Gibbs free energy), magnetic properties and solvation energies. It includes a variety of methods and basis sets for the calculations of different atomic or molecular properties. Some of the methods included within Gaussian software program are the Hartree Fock (HF) method, Semi-Empirical methods (e.g., Austin Model 1 (AM1) and Parameterised Model number 3 (PM3)), DFT, with various functionals that may include only the exchange term (e.g., MBJ), the correlation term (e.g., B96) or the hybrid functional that include both the exchange and the correlation terms (e.g., the B3LYP functional) and a number of *ab initio* methods such as *Møller–Plesset* (e.g., MP2) and CBS methods. Along with the methods, the software program also includes a variety of basis sets to choose from, such as the Pople type basis sets, Dunning's correlation consistent basis sets and density fitting basis sets.

The Gaussian program is subdivided into four different sections. The first section request the checkpoint file, which is a file that contains all the codes used for a calculation. The second section requests information on all the keywords required for the type of a job that has to be performed. This section is called the route section. For instance, if the job that has to be performed is optimisation, the keyword that is requested by Gaussian is “opt”; if the type of job that has to be performed is frequency calculation, the keyword that has to be inserted in the route section is “Freq”. Multiple keywords can also be inserted in the route section for instance the keyword “Opt freq” would request the Gaussian program to perform optimisation job followed by frequency calculation on the optimised structure, by requesting information from the checkpoint file. The third section is the title section, for which the user has the discretion to provide a name that would identify the type of calculation. The fifth section requires charge and multiplicity of the atom or the molecule to be calculated. The last section requires the specification of the structure in terms of coordinates of interest (e.g., internal and Cartesian coordinates).

The Gaussview program is a graphical interface linked to Gaussian program. It allows the use to be able to create input structures and determines all the required components in Gaussian program. Gaussview may either call Gaussian after the preparation of input by using an option “calculate” in Gaussview or the two programs may be used separately by filling up the subdivisions of Gaussian with structural information (in the form of coordinates) obtained from Gaussview. The Gaussview program is also capable of building any chemical structures (e.g., large molecular systems and ionic species) of interest; it can set up a calculation and view the results graphically while the Gaussian calculation is running and when the calculation has completed.

CHAPTER 3

COMPUTATIONAL DETAILS

3.1 Introduction and general information

In this chapter, the methods and approaches (procedures) that have been selected for the study reported in this dissertation will be presented and reasons for their selection will be explained. The selection of basis sets for the study is also discussed as well as the selection of the type of media in which the reactions were modelled is discussed. The approaches utilised to estimate the rate constants and the branching ratios will also be discussed. Lastly, the computational software programmes used in the study will be mentioned.

The relative energies of the reaction species were calculated relative to the sum of the energies of the individual non-interacting reactant species. The energy barriers were calculated as the difference between the energy of the transition state and the energy of the reactant complex. All calculations were performed at room temperature ($T = 278\text{ K}$) and utilising the standard pressure of 1 atm.

Geometry optimisations, frequency calculations and IRC calculations, were performed using the Gaussian09 program [244]. The geometries were drawn using the GaussView5 program. AIM analysis was performed using the QTAIM software program [235]. The schematic drawings were done using Chemdraw present in ChemOffice 10 [245].

3.2 Selection of the calculation methods and basis sets

Relaxed geometry optimisations for the reactants, transition states, intermediates and product species were performed with the density functional theory method by using three different functionals, two hybrid GGA functionals, which are BHHLYP [88, 246–249]

and MPW1K [250, 251] functionals and a hybrid metal-GGA, which is the M06-2X functional [103, 252]. The selected functionals are largely designed to account for thermochemistry, kinetics and estimation of equilibrium geometries of systems containing non-covalent interactions [90, 246–255]; reactant and product species for the systems investigated in this study are characterised by the presence of non-covalent interactions. Benchmark calculations utilising the CBS-QB3 compound method was selected for benchmarking the selected DFT methods in terms of their ability to estimate the barrier height energies for the studied reactions. Specifically, the testing was performed on the reactions involving $\bullet\text{OOH}$ with either FG or THAP molecule. The Pople 6-31++G(d,p) and the 6-311++G(3df,2p) basis sets were utilised for the investigation. Both basis sets include the polarisation and diffuse functions necessary for describing intermolecular interactions (taking place within the reactant and product complexes); diffuse functions are also considered values for describing the features of radical species. The selected basis sets are widely utilised in the study of chemical reactions, especially when characterising geometric features of transition state structures [256–261].

3.3 Procedure for the investigations of reaction mechanisms

3.3.1 Optimisation of isolated molecules and reactant species

The input structures for the isolated phloroglucinol, phloroacetophenone, hydroxyl radical and hydroperoxyl radical were generated in the Cartesian coordinate format. The calculations were performed by considering that for a neutral molecule the charge is 0 and the multiplicity is 1, for the neutral radical species, the charge is zero and the multiplicity is 2, for the cationic species, the charge is 1 and multiplicity is 2 and for an anionic species, the charge is -1 and multiplicity is 1.

The reactant complexes, specifically for the neutral species, were prepared by positioning the radical species in the vicinity of the H-bond donor or accept atom of the FG molecule so that the two atoms are within the bond distances that can be considered sufficient for intermolecular interactions between the two reactant species. For instance, in the DHAA mechanism; the radical species is arranged in close proximity to one of the phenolic

hydrogen atom, within reasonable distance to allow for O–H···O interactions. The Cartesian coordinates for the inputs were then generated and the optimisation of the input was performed by considering that for a molecule···neutral radical interactions, the charge is zero and the multiplicity is 2.

Calculations in the presence of the implicit solvent model were performed using the solvation model density (SMD). The two solvents that were selected for the study are benzene and ethanol.

Frequency calculations upon the optimised geometries (isolated molecules and reaction species) were performed at the same level of optimisation to obtain information on the signs of the eigenvalues obtained from solving the Hessian matrix. Non-negative frequencies values correspond to minima points on the potential surface while one imaginary frequency value corresponds to a first order saddle point (section 2.3).

Finally, IRC calculations were performed to determine if the transition states found connect the reactant complex and the product complex, or reactant complex and the intermediate species or the intermediate structure and the product structure. The IRC data on the calculated structures were extracted from the checkpoint files. Keywords “IRC”, “stepsise=n”, “maxpoints=n”, “geom-check” and either “forward” or “reverse” for the direction of the IRC path were used in the calculation.

3.3.2 Procedure for performing direct hydrogen abstraction mechanism

The reaction transition states (TSs); FG + •OH + FG + •OOH and THAP + •OOH were located through the minimum energy path scan of the selected intermolecular bonds within the reactant complex species (between the molecule of interest and the radical species). The intermolecular O···H bond (formed in each of the reactant species) was utilised to determine the reaction coordinates for the scan in the determination of the transition states. A similar approach for location of transition states has been utilised in other works [258–260]. The MEP scan was performed starting from the optimised reactant complex of phenolic compound (either FG or THAP) with specific radical species (•OH or •OOH) with the aim of abstracting the hydrogen atom from the phenolic

OH in order to form a relevant stable phenoxyl radical as the main product. The bond scan was performed in steps of 0.01Å. The highest point on the MEP was then optimised separately, with the inclusion of the keywords “TS”, “noeigentest” and “calcfc”, to locate the transition state.

3.3.3 Mechanism for the addition of the •OH on the phenolic ring

The addition mechanism was considered for FG + •OH and THAP + •OH. The reactant complexes were constructed using a similar approach used in section 3.3.1. The transition states (s) were also obtained from the MEP scan. The specific intermolecular bond that was scanned and used as reaction coordinates for finding the transition state (s) is the C...O bond. The MEP scan was performed with the purpose of adding the •OH to the non-hydroxyl substituted carbon atom in a selected phenolic compound (either FG or THAP). The MPE bond scan was also performed in steps of 0.01Å.

3.3.4 Water elimination in the absence and presence of a base

To eliminate a water molecule from the optimised tetrahydroxycyclohexadienyl radical species (which is a reactant in this mechanism), obtained in the addition mechanism (section 3.3.3), an MEP scan was performed in order to remove the hydrogen atom at the C_{sp³} atom and bonding it on the phenolic OH group present at either of the *ortho* positions with respect to the C_{sp³} atom. The bond scan was performed in steps of 0.01Å until the hydrogen atom on C_{sp³} was abstracted, resulting in the elimination of the water molecule and the formation of a relevant stable phenoxyl radical.

The mechanism for the abstraction of the water molecule from the intermediate in the presence of a base (OH⁻) required multiple steps. The first step of the mechanism was to perform a reaction involving tetrahydroxycyclohexadienyl radical species and the OH anion, in which the OH anion abstracts the H atom from the phenolic OH present at *ortho* position to the C_{sp³} atom. This reaction corresponds to deprotonation of the tetrahydroxycyclohexadienyl radical. The elimination of the OH anion from trihydroxycyclohexadienone anion radical, at the C_{sp³} atom, constituted the second step

of the overall reaction in the presence of the base. This step was also achieved by running a $C_{sp^3} - OH$ scan in step of $0.01\text{\AA}$ until the OH anion is completely eliminated from trihydroxycyclohexadienone anion radical.

3.3.5 Oxidation mechanism without and with the presence of O_2

The oxidation mechanism was performed, starting from tetrahydroxycyclohexadienyl radical, with the aim of obtaining a high order polyphenol compound (1, 2, 3, 5-tetrahydroxybenzene). A C–H scan was performed in order to remove the H atom from C_{sp^3} in the absence of any other reagent. The scan was performed in steps of $0.01\text{\AA}$. The highest point on the scan was assumed to be the possible transition state.

The oxidation mechanism in the presence of O_2 required multiple of steps. It was performed by utilising the O_2 whose spin multiplicity is 1. $^1O_2$ was chosen because the singlet oxygen reacts readily with organic molecule better than the triplet ($^3O_2$) oxygen molecule. The first step was to perform a $C\cdots O$ bond scan with the aim of adding O_2 molecule to the *ortho* position with respect to the C_{sp^3} atom of tetrahydroxycyclohexadienyl radical species obtained in section 3.3.3. The C atom in the $C\cdots O$ bond corresponds to the C atom at the *ortho* position with respect to the C_{sp^3} atom and the O atom is one of the O atoms of O_2 . The structure obtained after the addition of the O_2 molecule is hereby referred to as the first intermediate. The second step was to perform an $O\cdots H$ MEP scan starting from the optimised first intermediate, with the aim of eliminating $\bullet OOH$, by abstracting an H atom from phenolic OH bonded on the same carbon as the O_2 molecule, giving rise to the second intermediate. The third step is the isomerisation step; it starts from the second intermediate, and it is performed by running an $O\cdots H$ scan in order to remove the H atom on C_{sp^3} and bonding it covalently to the keto O atom, resulting in the formation of tetrahydroxybenzene.

3.3.6 Determination of reaction enthalpies for the reactions

The bond dissociation enthalpy (*BDE*), which describes the hydrogen atom transfer (HAT) mechanism, the ionisation potential (*IP*), which describes the single electron

transfer mechanism, the *IP* and the proton dissociation enthalpy (*PDE*), which together describes the single electron transfer-proton transfer (SET-PT) mechanism, and the proton affinity (*PA*) and electron transfer enthalpy (*ETE*), which together describes the sequential proton-loss electron-transfer (SPLET) mechanism, were calculated using specific equations for each radical...molecule reaction studied. For illustration purposes, we describe below the estimation of each of the thermodynamic parameters for the case of the reaction of $\bullet\text{OOH}$ and THAP molecule. The HAT mechanism was considered to occur through the reaction;



where $\text{THAP}\bullet$ represent the radical formed by abstraction of the phenolic H atom from THAP. The corresponding *BDE* was estimated following the equation;

$$H_{BDE} = H(\text{THAP}\bullet) + H(\text{H}_2\text{O}_2) - H(\bullet\text{OOH}) - H(\text{THAP}). \quad (3.2)$$

The SET-PT mechanism was considered to occur according to the following chemical equation;



where $\text{THAP}^{\bullet+}$ represent the cationic radical corresponding to the removal of the electron from THAP. The *IP* corresponding to this reaction was calculated as;

$$\Delta H_{IP} = H(\text{THAP}^{\bullet+}) + H(\text{OOH}^-) - H(\bullet\text{OOH}) - H(\text{THAP}). \quad (3.4)$$

The proton transfer step was considered to occur through the reaction in which the radical cation transfers a proton to OOH^- ;



PDE parameter for this reaction was estimated using the equation;

$$\Delta H_{PDE} = H(\text{THAP}^\bullet) + H(\text{H}_2\text{O}_2) - H(\text{THAP}^{\bullet+}) - H(\text{OOH}^-). \quad (3.6)$$

The first step of SPLET mechanism was considered to occur through the following reaction;



where THAP^- denotes the anionic species resulting from the deprotonation of THAP. The PA value controlling this reaction step was estimated using the equation;

$$\Delta H_{PA} = H(\text{THAP}^-) + H(\text{H}_2\text{O}_2) - H(\text{THAP}) - H(\text{OOH}^-). \quad (3.8)$$

The second step for the SPLET mechanism was considered to occur through the following chemical reaction;



The ETE , which control this reaction, was estimated by using the equation

$$\Delta H_{ETE} = H(\text{THAP}^\bullet) + H(\text{OOH}^-) - H(\text{THAP}^-) - H(\bullet\text{OOH}). \quad (3.10)$$

3.4 Calculation of the reaction rate constants

The rate constants for the individual steps within a given reaction mechanism (e.g., direct hydrogen atom removal, addition mechanism, water elimination mechanism in the presence and absence of the base catalyst and oxidation mechanism in the presence and absence of the O_2 molecule) were calculated using the Eyring equation (equation 2.126). In solution, the rate constant (k_{act}) was calculated using equation 2.151. The diffusion rate constant (k_D) value for the reaction of $\bullet\text{OH}$ and FG molecule in solution was estimated using the equations;

$$k_D = 4\pi R_{PG\bullet OH} D_{PG\bullet OH} N_A, \quad (3.11)$$

where FG and $\bullet OH$ represent interacting molecules; FG is assumed to have a radius of R_{PG} while $\bullet OH$ has a radius of $R_{\bullet OH}$. The acronym $D_{PG\bullet OH}$ denotes the sum of the diffusion coefficients of the two reactant species in solution. The diffusion coefficients for isolated reactant species were calculated using equations;

$$D_{PG} = \frac{k_B T}{6\pi\eta R_{PG}} \quad \text{and} \quad D_{\bullet OH} = \frac{k_B T}{6\pi\eta R_{\bullet OH}}, \quad (3.13)$$

where the viscosity value of benzene is 6.011×10^{-4} Pas and the viscosity of ethanol is and 1.095×10^{-3} Pas.

3.5 Quantum Theory of Atoms in Molecules

QTAIM program was utilised to obtain bond critical point data that are crucial for understanding the bonding properties of the pre-reactive complex, transition state structures, intermediate structure and product complex species. The molecular graphs were constructed from the formatted checkpoint files to provide information on the presence of any intermolecular interactions between the two reactant molecules within the reactant complex, or between the product molecules within the product complex.

The bond critical point data (such as the electron density and the corresponding Laplacian) for the selected bonds was obtained from QTAIM calculations and reported in a form of a table for the purpose of utilising them to understand the electronic and other features of the reaction species. The total electron density energy of the optimised geometries (i.e., reactant complex structure, transition state structure, intermediate structure and product complex species) was calculated as the sum of the potential and kinetic electron density energies.

CHAPTER 4

REACTIONS OF PHLOROGLUCINOL AND PHLOROACETOPHENONE WITH $\bullet\text{OH}$

4.1 Introduction

This chapter presents and discusses the results obtained for the reaction of phloroglucinol and phloroacetophenone with $\bullet\text{OH}$. Phloroglucinol (FG) has two possible conformers; the conformation having the C_{3h} symmetry is the most stable configuration [262, 263]. The present study only reports the results of the investigation on the reactions of $\bullet\text{OH}$ with the FG conformation having the C_{3h} symmetry.

Conformations of THAP have also been reported in previous studies, with the findings suggesting that the preferred conformations are those in which the molecule forms intramolecular hydrogen bond involving the *keto* group in the *acyl* chain and the neighbouring *ortho* phenolic OH group [263]. The phenolic OH involved in intramolecular hydrogen bond is not easily available for interaction with $\bullet\text{OH}$ [264, 265]. Therefore, there are only two possible sites through which THAP may react with $\bullet\text{OH}$, which are the *para* phenolic OH and the free *ortho* phenolic OH. This analysis is confirmed by experimental findings on the reaction of THAP with some radical species, in which it was found that the sites of reactivity are the *para* phenolic OH and *ortho* phenolic OH sites [68, 69]. The two reactive sites on THAP are denoted throughout this dissertation with abbreviation THAP1 for the *ortho* site and THAP2 for the *para* phenolic OH site.

In chapter two (section 2.4), it was indicated that antioxidant molecules may scavenge radical species through hydrogen atom transfer (HAT), single electron transfer-proton transfer (SET-PT) and sequential proton loss-electron transfer (SPLET) mechanisms.

However, the reactions of phloroglucinol derivatives with $\bullet\text{OH}$ is not limited to the HAT mechanisms but can also proceed through the oxidation mechanism, in which the initial phloroglucinol molecule is transformed into a polyphenolic molecule. All the different mechanisms were investigated on the reaction of FG and THAP with $\bullet\text{OH}$ in order to identify the preferred mechanism. The initial part of the presentations in this chapter (section 4.2) is related to the results of the thermodynamic parameters (i.e., reaction enthalpies) related to the different reaction mechanisms.

The HAT mechanism for polyphenolic derivatives is known to proceed through different pathways (section 1.2); the different mechanistic pathways are described in this chapter for both FG and THAP. Section 4.3 reports the results of the findings on the HAT mechanism for the FG + $\bullet\text{OH}$ reaction while section 4.4 reports the results of the findings on the HAT mechanism for the THAP + $\bullet\text{OH}$ reaction; The last part of the chapter (section 4.5) provides a comparison of the results obtained utilising different calculation methods as well as a comparison with the available experimental data.

The geometry features are not different among the different methods, therefore, only the geometries of M06–2X/6-311++G(3df,2p) obtained in gaseous phase are shown. In a case whereby there is a significance difference between the geometry features (e.g., significant torsion angle differences between results of one method and results of another method), both geometries obtained with different methods are shown.

4.2 Reaction enthalpies related to HAT, SET-PT and SPLET mechanisms for the reaction between FG and THAP with $\bullet\text{OH}$

The reaction enthalpies for the HAT mechanism (bond dissociation enthalpy (*BDE*)), SET-PT mechanism (ionisation potential (*IP*) and proton affinity (*PA*)) and SPLET mechanism (proton dissociation enthalpy (*PDE*) and electron transfer enthalpy (*ETE*)), are reported in Table 4.1 and Table 4.2 for the results obtained utilising 6-31++G(d, p) and 6-311++G(3df, 2p) basis sets, respectively.

Table 4.1: Reaction enthalpy values (kcal/mol) for FG + •OH and THAP + •OH; the results are obtained by using the 6-31++G(d, p) basis set.

structure ^a	HAT ^b	SET-PT ^b		SPLET ^b	
	ΔH_{BDE}^c	ΔH_{IP}^c	ΔH_{PDE}^c	ΔH_{PA}^c	ΔH_{ETE}^c
DFT/M06-2X results obtained <i>in vacuo</i>					
FG	-25.728	154.995	-180.723	-47.063	21.535
THAP1	-28.238	153.740	-181.978	-63.378	35.755
THAP2	-21.963	153.740	-97.891	-60.868	39.436
DFT/M06-2X results obtained in benzene medium					
FG	-26.983	88.479	-115.462	-34.513	7.686
THAP1	-28.238	87.851	-116.089	-47.063	18.499
THAP2	-21.963	87.851	-110.442	-45.181	22.748
DFT/M06-2X results in ethanol medium					
FG	-29.493	18.198	-47.691	-17.570	36.610
THAP1	-30.120	20.080	-50.201	-23.218	42.079
THAP2	-24.473	20.080	-44.553	-23.218	47.431
DFT/MPW1K results obtained <i>in vacuo</i>					
FG	-26.355	155.622	-181.978	-47.063	20.862
THAP1	-27.610	90.361	-117.972	-63.378	35.677
THAP2	-20.708	90.361	-97.891	-60.868	39.893
DFT/MPW1K results obtained in benzene medium					
FG	-27.610	88.479	-108.559	-34.513	7.422
THAP1	-28.238	89.106	-117.344	-47.063	18.707
THAP2	-21.335	89.106	-110.442	-45.181	23.433
DFT/MPW1K results obtained in ethanol medium					
FG	-29.493	20.708	-48.946	-16.943	36.749
THAP1	-29.493	21.335	-50.828	-23.218	42.940
THAP2	-22.590	21.335	-43.926	-23.218	49.438
DFT/BHLLYP results obtained <i>in vacuo</i>					
FG	-25.728	154.995	-180.723	-45.181	19.524
THAP1	-26.983	155.622	-182.605	-61.496	34.437
THAP2	-20.708	155.622	-97.891	-59.613	38.253
DFT/BHLLYP results obtained in benzene medium					
FG	-26.983	87.851	-114.834	-32.630	5.835
THAP1	-27.610	88.479	-116.089	-45.181	17.221
THAP2	-21.963	88.479	-110.442	-43.298	21.551
DFT/BHLLYP results obtained in ethanol medium					
FG	-29.493	18.825	-48.318	-15.060	34.895
THAP1	-29.493	20.708	-50.201	-21.335	41.434
THAP2	-23.845	20.708	-44.553	-21.335	46.622

^a The abbreviations FG, THAP stand for phloroglucinol and 2, 4, 6-trihydroxyacetophenone respectively. The arabic numerals "1" and "2" after the abbreviation THAP represent the *ortho* phenolic OH reaction site and the *para* phenolic OH reaction site respectively.

^b The abbreviations HAT, SET-PT and SPLET stands for hydrogen atom transfer mechanism, single electron-proton transfer mechanism and sequential proton loss-electron transfer mechanism respectively.

^c The acronym H_{BDE} stands for bond dissociation enthalpy, H_{IP} stands for ionization potential energy, H_{PA} proton affinity, H_{PDE} stands for proton dissociation enthalpy and H_{ETE} stands for electron transfer enthalpy.

Table 4.2: Reaction enthalpy values (kcal/mol) for FG + •OH and THAP + •OH; the results are obtained by using the 6-311++G(3df, 2p) basis set.

structure ^a	HAT ^b	SET-PT ^b		SPLET ^b	
	ΔH_{BDE} ^c	ΔH_{IP} ^c	ΔH_{PDE} ^c	ΔH_{PA} ^c	ΔH_{ETE} ^c
DFT/M06–2X results obtained <i>in vacuo</i> medium					
FG	–26.355	88.479	–114.834	–48.318	21.678
THAP1	–28.865	153.740	–182.605	–64.006	35.306
THAP2	–23.218	153.740	–99.774	–62.123	38.844
DFT/M06–2X results obtained in benzene medium					
FG	–28.238	87.851	–116.089	–35.768	7.883
THAP1	–29.493	87.851	–117.344	–47.691	18.303
THAP2	–23.845	87.851	–111.697	–45.808	22.263
DFT/M06–2X results obtained in ethanol medium					
FG	–29.493	18.825	–48.318	–16.943	36.055
THAP1	–30.748	20.080	–50.828	–23.845	41.401
THAP2	–24.473	20.080	–44.553	–23.218	47.371
DFT/MPW1K results obtained <i>in vacuo</i> medium					
FG	–26.983	89.106	–116.089	–47.691	20.806
THAP1	–28.865	154.367	–183.233	–64.006	35.087
THAP2	–21.963	154.367	–98.519	–61.496	39.719
DFT/MPW1K results obtained in benzene medium					
FG	–28.238	87.851	–116.089	–35.141	7.447
THAP1	–28.865	87.851	–116.717	–47.063	18.283
THAP2	–22.590	87.851	–110.442	–45.181	23.303
DFT/MPW1K results obtained in ethanol medium					
FG	–30.120	18.825	–48.946	–16.943	35.959
THAP1	–29.493	20.708	–50.828	–22.590	41.908
THAP2	–23.218	20.708	–43.926	–22.590	48.400
DFT/BHLLYP results obtained <i>in vacuo</i> medium					
FG	–26.355	87.851	–114.207	–45.808	19.713
THAP1	–27.610	154.367	–182.605	–61.496	34.086
THAP2	–21.335	154.995	–99.146	–59.613	38.311
DFT/BHLLYP results obtained in benzene medium					
FG	–27.610	87.224	–114.834	–33.885	6.140
THAP1	–28.865	88.479	–117.344	–45.181	17.084
THAP2	–21.963	88.479	–111.069	–43.926	23.303
DFT/BHLLYP results obtained in ethanol medium					
FG	–30.120	18.198	–48.318	–15.688	34.450
THAP1	–29.493	20.080	–49.573	–21.963	40.851
THAP2	–23.218	20.080	–43.298	–21.963	46.488

^a The abbreviations FG, THAP stand for phloroglucinol and 2, 4, 6-trihydroxyacetophenone respectively. The arabic numerals “1” and “2” after the abbreviation THAP represent the *ortho* phenolic OH reaction site and the *para* phenolic OH reaction site respectively.

^b The abbreviations HAT, SET-PT and SPLET stands for hydrogen atom transfer mechanism, single electron-proton transfer mechanism and sequential proton loss-electron transfer mechanism respectively.

^c The acronym H_{BDE} stands for bond dissociation enthalpy, H_{IP} stands for ionization potential energy, H_{PA} proton affinity, H_{PDE} stands for proton dissociation enthalpy and H_{ETE} stands for electron transfer enthalpy.

4.2.1 Analysis of the *BDE* values for the HAT mechanism

The *BDE* values for $\text{FG} + \bullet\text{OH}$ and $\text{THAP} + \bullet\text{OH}$ are all negative, indicating that the reactions of FG and THAP with $\bullet\text{OH}$ through the HAT mechanism are exothermic in nature. The implication of the findings reported here is that the HAT mechanism is thermodynamically favoured. The fact that the *BDE* values obtained are negative, agrees with other findings on the reaction of flavonoids with $\bullet\text{OH}$ [266, 267]. In other words, it appears that reactivity of polyphenol derivatives towards $\bullet\text{OH}$ is a thermodynamically favoured process.

The *BDE* value (kcal/mol) obtained using the M06–2X/6-311++G(3df, 2p), for the results *in vacuo*, for $\text{THAP2} + \bullet\text{OH}$ is 2.51 and 5.647 higher than the *BDE* value corresponding to $\text{FG} + \bullet\text{OH}$ as well as $\text{THAP1} + \bullet\text{OH}$ respectively, indicating that $\text{THAP2} + \bullet\text{OH}$ is less thermodynamically preferred to $\text{FG} + \bullet\text{OH}$ and $\text{THAP1} + \bullet\text{OH}$. The implication of this finding is that $\bullet\text{OH}$ scavenging ability of THAP at the *para* phenolic OH position is less than its $\bullet\text{OH}$ scavenging ability at the *ortho* phenolic OH position. These results are in agreement with experimental data reported on the two compounds [68, 69], which report that the antiradical activity of THAP at the *para* phenolic OH position is less than the antiradical activity of THAP at the *ortho* phenolic OH. *BDE* values corresponding to $\text{THAP1} + \bullet\text{OH}$ are lower than for $\text{FG} + \bullet\text{OH}$, indicating that THAP has a higher tendency to scavenge $\bullet\text{OH}$ than FG, a result that is also consistent with experimental data [68, 69].

The results obtained in the non-polar medium and the polar medium follow a similar trend as the results obtained *in vacuo*. The *BDE* values for $\text{FG} + \bullet\text{OH}$ in different media decrease with an increase in solvent polarity. This result implies that the $\text{FG} + \bullet\text{OH}$ reaction performed in a polar solvent is more thermodynamically preferred to occur than when performed in non-polar solvent or *in vacuo*. The results obtained for $\text{THAP1} + \bullet\text{OH}$ and $\text{THAP2} + \bullet\text{OH}$ in different media follows the same trend as $\text{FG} + \bullet\text{OH}$. In other words, within the biological systems, the HAT mechanism is likely to occur within the aqueous medium environment than within the fatty lipid medium environment, which is characterised largely as a non-polar medium.

4.2.2 Analysis of the *IP* and *PDE* values for the SET-PT mechanism

The *IP* values are all greater than zero for both FG + •OH and THAP + •OH, which implies that the SET step in the SET-PT mechanism is endothermic in nature, which further implies that this step is not thermodynamically favoured. The results reported here are also in agreement with the previous findings for the reactions of flavonoids with •OH [266, 267], which reported the *IP* values for the reactions to be positive and relatively large. The *PDE* values, which provide information on the reactivity of the second step of the SET-PT mechanism, are negative for all the studied reactions, indicating that the PT step is exothermic. However, the PT step is not considered as the rate-limiting step in SET-PT; rather, the rate-limiting step is the step controlled by the *IP*.

A comparison between the *IP* values for SET and *BDE* value for HAT suggests that the *IP* values are significantly higher than the *BDE* values for all the reactions in different media, implying that the HAT mechanism is preferred to SET; this is also a conclusion reached in other studies of the reactions of polyphenolic derivatives with •OH [266, 267].

The *IP* values, within a given medium, show different trends; the *IP* value for FG + •OH *in vacuo* is significantly lower than the *IP* value for THAP + •OH in most cases, indicating that less energy is needed to transfer an electron in FG + •OH than in THAP + •OH. The implication of the results is that THAP + •OH is less preferred to occur *in vacuo* through the SET-PT mechanism in comparison to FG + •OH. The *IP* values obtained in benzene does not show particular preference for the electron transfer in FG + •OH and in THAP + •OH. Finally, the *IP* values obtained in ethanol medium suggest slight preference for the FG + •OH to THAP + •OH. The *IP* values for THAP2 + •OH and THAP1 + •OH show no significant difference in all the media, implying that the *IP* values for THAP + •OH minimally depend on the reaction site.

The *IP* value for FG + •OH across media decreases with an increase in dielectric constant, suggesting that an electron is easily transferred in a polar medium than in non-polar medium. A similar trend is also observed for THAP + •OH in different media.

The product of the single electron transfer step is the cation radical $\text{FG}^{\bullet+}$ and $\text{THAP}^{\bullet+}$ for $\text{FG} + \bullet\text{OH}$ and $\text{THAP} + \bullet\text{OH}$, respectively. The second step of the reaction which corresponds to $\text{FG}^{\bullet+} + \text{OH}^-$ and $\text{THAP}^{\bullet+} + \text{OH}^-$ are controlled by *PDE* (kcal/mol), whose values are -114.834 for $\text{FG}^{\bullet+} + \text{OH}^-$, -182.605 for $\text{THAP1}^{\bullet+} + \text{OH}^-$ and -99.774 for $\text{THAP2}^{\bullet+} + \text{OH}^-$ (using M06-2X/6-311++G(3df, 2p) *in vacuo*). The *PDE* value for $\text{THAP2}^{\bullet+} + \text{OH}^-$ is significantly higher than the *PDE* values for $\text{FG}^{\bullet+} + \text{OH}^-$ and for $\text{THAP1}^{\bullet+} + \text{OH}^-$. Furthermore, between $\text{FG}^{\bullet+} + \text{OH}^-$ and $\text{THAP}^{\bullet+} + \text{OH}^-$, the preferred reaction for the proton transfer is $\text{THAP}^{\bullet+} + \text{OH}^-$. Moreover, analysis of the *PDE* values for $\text{THAP1}^{\bullet+} + \text{OH}^-$ and $\text{THAP2}^{\bullet+} + \text{OH}^-$ indicates that proton transfer is likely to occur at the *ortho* phenolic OH position than at the *para* phenolic OH position.

Analysis of the results in benzene and in ethanol media suggests that similar trends are obtained as that obtained *in vacuo*, which is to say that $\text{THAP}^{\bullet+} + \text{OH}^-$ has lower *PDE* value than $\text{FG}^{\bullet+} + \text{OH}^-$ in and that $\text{THAP1}^{\bullet+} + \text{OH}^-$ gives lower *PDE* value than $\text{THAP2}^{\bullet+} + \text{OH}^-$. The implication of this analysis is that in all the media, proton transfer is likely to occur at the *ortho* phenolic OH position than at the *para* phenolic OH position.

Analysis of the *PDE* values for a given reaction (e.g., $\text{FG}^{\bullet+} + \text{OH}^-$ or $\text{THAP}^{\bullet+} + \text{OH}^-$) in different media indicates that they are lowest in non-polar medium (benzene) and highest in polar medium. It is therefore possible to infer that the proton transfer reaction is likely to take place in a non-polar medium than *in vacuo* or in a polar medium. A similar trend is observed when comparing the difference in the site reactivity for THAP, which is performed by comparing the *PDE* values for $\text{THAP1}^{\bullet+} + \text{OH}^-$ and $\text{THAP2}^{\bullet+} + \text{OH}^-$ in different media.

4.2.3 Analysis of the *PA* and *ETE* values for the SPLET mechanism

The first step of the SPLET mechanism requires the proton loss from the neutral species (i.e., FG or THAP) to an anionic OH species, to form polyphenolic anionic species and hydrogen peroxide molecules as products. This step is controlled by *PA*, however, the proton loss step is not considered as the rate-limiting step in the SPLET mechanism; rather, the rate-limiting step is the electron transfer step of the mechanism. The *PA* values

for $\text{FG} + \text{OH}^-$ and $\text{THAP} + \text{OH}^-$ are all less than zero, suggesting that the proton loss step is an energy releasing process in nature.

A comparison of the PA values obtained for the different reactions sites of THAP, which are assessed through consideration of $\text{THAP1} + \text{OH}^-$ and the $\text{THAP2} + \text{OH}^-$, show that $\text{THAP1} + \text{OH}^-$ is preferred to $\text{THAP2} + \text{OH}^-$, which suggests that the proton loss step in the THAP molecule may involve the *ortho* phenolic OH. Reactivity, at either reaction site, is influenced by the medium (it is higher in non-polar medium and lower in non-polar medium). Reactivity for $\text{FG} + \text{OH}^-$ is also media dependent, suggesting that the proton loss step is preferred to occur in non-polar medium. A comparison of the PA values obtained for $\text{FG} + \text{OH}^-$ and $\text{THAP} + \text{OH}^-$ suggests that the proton loss step is higher in $\text{THAP} + \text{OH}^-$ than in $\text{FG} + \text{OH}^-$ all the media; the difference it is more pronounced *in vacuo* than in the other two media.

The ETE values, for all the studied reactions are positive; this implies that the electron transfer step in the SPLET mechanism is not thermodynamically favoured. The results obtained are also in agreement with the previous findings for the reaction of flavonoids with $\bullet\text{OH}$ [266, 267]; which report the ETE values to be positive. An analysis of the ETE values obtained from the reactions of the anion species, resulting from the proton loss step, with $\bullet\text{OH}$ indicates that the electron transfer is preferred in the anion in which the proton loss occur at the *ortho* site. The ETE values also suggest that the electron transfer mechanism is most preferred in benzene medium and least preferred in ethanol medium. A comparison of the ETE values across structures suggests that $\text{FG}^- + \bullet\text{OH}$ gives a lower ETE value than $\text{THAP}^- + \bullet\text{OH}$, indicating that the SPLET mechanism is likely to occur in the FG molecule than in the THAP molecule. The reactivity preference for FG over THAP through the SPLET mechanism is media dependent.

The SET-PT mechanism and the SPLET mechanism are controlled by IP and ETE , respectively. ETE values are significantly lower than the IP values *in vacuo* and in benzene; however, they are higher than the IP values in ethanol. These results indicate that there is preference for the SET-PT mechanism to the SPLET mechanism in polar medium and minimal preference for it in non-polar medium. The BDE values *in vacuo*

and in benzene are lower than the ETE values, indicating that there is a preference for the HAT mechanism over the SPLET mechanism in non-polar medium. Moreover, the *BDE* values obtained in ethanol are also significantly lower than the *IP* values, suggesting that the HAT mechanism is preferred to electron transfer mechanism in polar medium. Therefore, in all the media utilised in this study, the selected phloroglucinol molecules appear to preferably react with $\bullet\text{OH}$ through the HAT mechanism.

Consideration of the results obtained, in respect of the analysis of the reaction enthalpies, as well as taking into consideration the findings of other studies, allows an inference that phloroglucinol and its derivatives scavenge $\bullet\text{OH}$ through the hydrogen atom transfer mechanism. For this reason, attention of the subsequent sections is on determining the different pathways associated with the hydrogen atom transfer mechanism. All the three phenolic OH groups are identical in the C_{3h} symmetry of phloroglucinol, so that a study on the abstraction of the phenolic H atom on a particular phenolic OH is sufficient to provide necessary information on the reactivity of phloroglucinol with $\bullet\text{OH}$. In the case of the THAP molecule, the two reactive sites are the *para* phenolic OH and *ortho* phenolic OH. However, a study on the reactivity of the *para* phenolic OH in THAP with $\bullet\text{OH}$ would provide similar information as information that would be obtained on the reactivity of either phenolic OH in FG with $\bullet\text{OH}$, since the environment (e.g., steric effects) around the *para* phenolic OH within THAP is similar to the environment about each phenolic OH in FG. Therefore, for the sake of brevity, the results of the THAP + $\bullet\text{OH}$ reaction, in relation to the HAT mechanism, is concerned with the reactivity of the free *ortho* phenolic OH rather than the free *para* phenolic OH.

4.3 FG + $\bullet\text{OH}$ reaction mechanism

This section presents the results of the HAT mechanism through the two different pathways, which were introduced in section 1.2. However, FG + $\bullet\text{OH}$ is not only limited to proceed through the HAT type of mechanism; it can also proceed through oxidation mechanism, resulting in the formation of 1,2,3,5-tetrahydroxybenzene [50]. The results

of all the different pathways are considered and presented in a manner in which the trends across geometric, energetic and electronic parameters are analysed.

4.3.1 Direct hydrogen atom abstraction (DHAA) mechanism

The reaction of FG with $\bullet\text{OH}$ was initiated by considering that it proceeds through the formation of the reactant complex $\text{FG}\cdots\bullet\text{OH}$. The reactant complex for the DHAA mechanism is denoted as $(\text{RC})_{\text{abs}}$ throughout the study. The optimised geometries of the $(\text{RC})_{\text{abs}}$ complexes in different media are shown in Figure 4.1; the figure also includes all other reaction species for the mechanism. The geometric properties (i.e., bond lengths, bond angles and torsion angles) of the reaction species are reported in Table 4.3.

The interaction of the free phenolic hydrogen atom (H7) and the oxygen atom of the radical species (O10) in the $(\text{RC})_{\text{abs}}$ complex leads to the formation of the intermolecular $\text{O10}\cdots\text{H7}$ hydrogen bond interaction holding the complex monomer units. In comparison with the free phenolic OH groups in the phloroglucinol molecule; the O7-H7 bond in $(\text{RC})_{\text{abs}}$ is elongated with respect to its value in the free phloroglucinol molecule and it is characterised by the decrease in the $\omega(\text{O7-H7})$ stretching vibrational frequency, and an IR intensity increase of the stretching vibration; the $\omega(\text{O7-H7})$ stretching vibrational frequency decreases from 3898 cm^{-1} to 3812 cm^{-1} while the IR intensity of the stretching vibration increases from 95 km/mol to 395 km/mol . The decrease in the stretching vibrational frequency is a characteristic utilised to identify the presence of hydrogen bonds and it is referred to as the red shift [268].

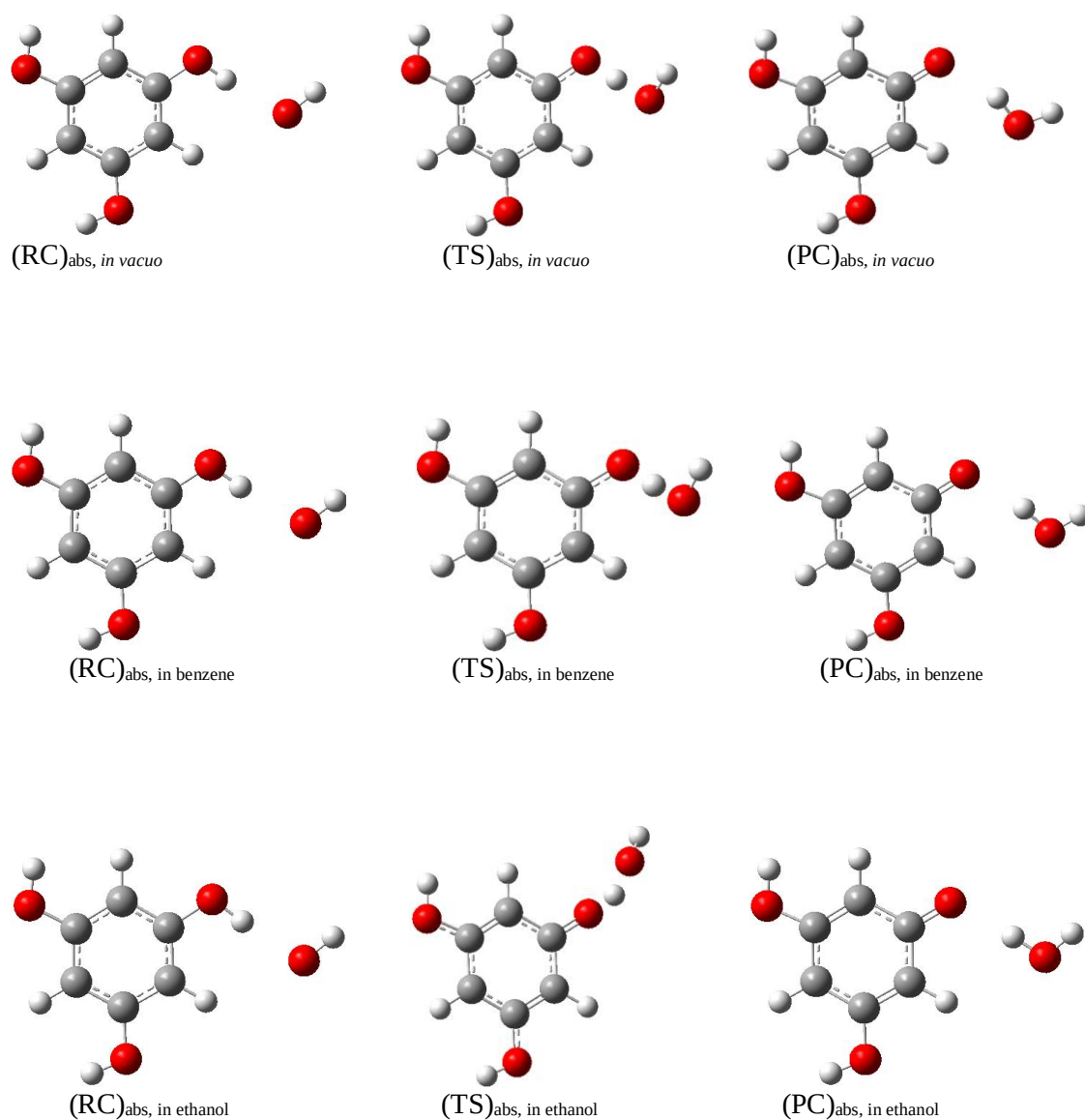


Figure 4.1: Reaction species for FG + •OH through the DHAA mechanism. M06–2X/6-311++G(3df,2p) results in different media. The abbreviation RC stands for reactant complex, TS stands for transition state and PC stands for product complex. The colour code red represents the oxygen atom, grey represents the carbon atom and white represents the hydrogen atom.

Table 4.3: Representative bond length (Å), bond angles (°) and torsion angles (°) for the FG + •OH reaction species obtained through the DHAA mechanism.

structure ^a and parameters	DFT/M06-2X			DFT/MPW1K			DFT/BHHLYP		
	<i>in vacuo</i>	<i>in benzene</i>	<i>in ethanol</i>	<i>in vacuo</i>	<i>in benzene</i>	<i>in ethanol</i>	<i>in vacuo</i>	<i>in benzene</i>	<i>in ethanol</i>
results with the standard basis set (6-31++G(d,p))									
(RC) _{abs}									
C2-O7	1.357	1.355	1.360	1.345	1.343	1.348	1.389	1.347	1.352
O7-H7	0.969	0.970	0.976	0.961	0.962	0.968	0.959	0.960	0.966
O10...H7	1.972	1.949	1.905	1.956	1.936	1.884	1.969	1.953	1.900
O7H7O10	175	176	179	170	171	175	173	172	172
C2O7H7O10	180	-180	-180	180	180	180	-180	-180	-180
(TS) _{abs}									
C2-O7	1.341	1.341	1.282	1.321	1.321	1.277	1.323	1.323	1.259
O7...H7	1.028	1.029	1.238	1.039	1.039	1.039	1.052	1.047	1.171
O10...H7	1.403	1.407	1.335	1.348	1.348	1.267	1.319	1.335	1.319
O7H7O10	150	150	157	156	156	156	157	157	180
C2O7H7O10	-85	-87	-88	-89	-90	-89	-85	-89	79
(PC) _{abs}									
C2-O7	1.254	1.255	1.259	1.246	1.247	1.251	1.248	1.248	1.251
O7...H7	1.906	1.881	1.851	1.883	1.882	1.843	1.908	1.888	1.849
O10-H7	0.972	0.973	0.976	0.963	0.964	0.968	0.963	0.964	0.967
O7H7O10	156	162	175	180	180	180	160	174	178
C2O7H7O10	0	0	3	-92	-92	-98	0	0	0
results with the extended basis set (6-311++G(3df,2p))									
(RC) _{abs}									
C2-O7	1.352	1.351	1.355	1.340	1.338	1.342	1.343	1.342	1.346
O7-H7	0.965	0.967	0.972	0.957	0.959	0.964	0.955	0.956	0.962
O10...H7	1.962	1.944	1.901	1.966	1.945	1.884	1.979	1.961	1.907
O7H7O10	174	173	176	167	169	173	169	170	171
C2O7H7O10	180	180	-180	-180	180	-180	-180	-180	-170
(TS) _{abs}									
C2-O7	1.341	1.336	1.274	1.316	1.317	1.270	1.317	1.318	1.260
O7...H7	1.028	1.027	1.240	1.037	1.034	1.039	1.050	1.044	1.167
O10...H7	1.403	1.402	1.336	1.346	1.358	1.265	1.317	1.333	1.319
O7H7O10	150	151	157	156	156	156	158	158	180
C2O7H7O10	-85	-88	-88	-89	-92	-89	-85	-88	-79
(PC) _{abs}									
C2-O7	1.243	1.245	1.250	1.237	1.237	1.242	1.237	1.237	1.241
O7...H7	1.898	1.874	1.843	1.894	1.888	1.843	1.911	1.895	1.851
O10-H7	0.969	0.970	0.973	0.961	0.961	0.965	0.959	0.960	0.963
O7H7O10	160	170	176	165	180	180	163	174	178
C2O7H7O10	0	-2	4	2	-90	-96	0	2	0

^aThe abbreviation RC denotes reactant complex, TS denotes transition state and PC denotes product complex.

There are minimal differences in the geometrical properties of (RC)_{abs} obtained in different media, indicating that the addition of the solvent has minimal effect on the structural features of (RC)_{abs}. However, the intermolecular hydrogen bond is influenced by the change in media; the O10...H7 bond distance (Å) is 1.962 *in vacuo*, 1.944 in non-polar medium and 1.901 in polar medium, implying that the O10...H7 bond distance tends to shorten significantly with the increase in the dielectric constant of the media, which further implies that the strength of the O10...H7 bond increases with the increase in

solvent polarity [269]. The $\text{O7}-\hat{\text{H7}}-\text{O10}$ bond angle is within a range of $167^\circ-179^\circ$, suggesting that the hydrogen bond is close to a linear arrangement of its atoms, which is a favourable arrangement for intermolecular hydrogen bond [270, 271]. The $\text{C2}-\text{O7}-\text{H7}-\text{O10}$ torsion angle obtained is approximately 180° in all media, implying that the solvent has minimal effect on the $\text{C2}-\text{O7}-\text{H7}-\text{O10}$ torsion angle.

The molecular graphs for $(\text{RC})_{\text{abs}}$, are shown in Figure 4.2. The results show the existence of the $\text{O10}\cdots\text{H7}$ intermolecular hydrogen bond in $(\text{RC})_{\text{abs}}$, what is in agreement with the earlier analysis on the geometric parameters.

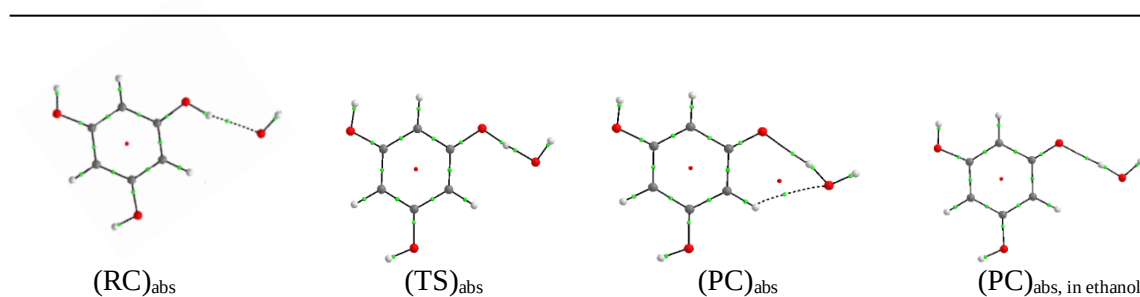


Figure 4.2: Molecular graphs for the $\text{FG} + \bullet\text{OH}$ reaction species obtained through the DHAA mechanism. The colour code red represents the oxygen atom, grey represents the carbon atom and white represents the hydrogen atom. The green dot across a bond represent a bond critical point while the red dot within a ring represent a ring critical point.

The electronic properties at the bond critical points (BCPs) are reported in Table 4.4. $\nabla^2\rho$, G and H are all positive for the $\text{O10}\cdots\text{H7}$ bond in $(\text{RC})_{\text{abs}}$, suggesting that the bond has a weak intermolecular bond character in nature. The ρ value increases with an increase in solvent polarity, implying that the $\text{O10}\cdots\text{H7}$ bond becomes stronger with the increase in solvent polarity. The $\nabla^2\rho$ and H values for the $\text{O7}-\text{H7}$ bond are negative, indicating that the $\text{O7}-\text{H7}$ bond is covalent in nature. $\nabla^2\rho$ and H values decrease with an increase in dielectric constant of the media, implying that the $\text{O7}-\text{H7}$ bond in $(\text{RC})_{\text{abs}}$ tends to weaken in polar medium than *in vacuo* or in non-polar medium.

Table 4.4: Electronic properties (density and energy) at the bond critical points for selected bonds within the FG + •OH reaction species obtained through the DHAA mechanism.

structure ^a and bond distance	electron density ρ ($e\text{\AA}^3$)	Laplacian of the electron density $\nabla\rho^2$ ($e\text{\AA}^5$)	Potential electron energy density V (Hartree)	Kinetic electron energy density G (Hartree)	Total electron energy density H (Hartree)
results in vacuum medium					
(RC) _{abs}					
C2–O7	0.308643	–0.532766	–0.852851	0.359830	–0.493020
O7–H7	0.377770	–2.973919	–0.882850	0.069685	–0.813170
O10...H7	0.022004	0.080046	–0.016974	0.018492	0.001518
(TS) _{abs}					
C2–O7	0.327468	–0.479605	–0.958177	0.419138	–0.539040
O7...H7	0.270616	–1.613186	–0.588018	0.092361	–0.495660
O10...H7	0.120275	0.078947	–0.150392	0.085064	–0.065330
(PC) _{abs}					
C2–O7	0.401577	–0.433690	–1.347448	0.619513	–0.727940
O7...H7	0.026222	0.093285	–0.021293	0.022307	0.001014
O10–H7	0.370895	–2.889400	–0.864797	0.071223	–0.793570
O10...H3	0.007576	0.031197	–0.005194	0.006497	0.001303
results in benzene medium					
(RC) _{abs}					
C2–O7	0.293696	–1.107112	–0.3658	0.044528	–0.321310
O7–H7	0.292370	–1.096725	–0.364497	0.045158	–0.319340
O10...H7	0.292517	–1.097870	–0.364733	0.045133	–0.319600
(TS) _{abs}					
C2–O7	0.326186	–0.473811	–0.953578	0.417563	–0.536020
O7...H7	0.275332	–1.688308	–0.603549	0.090736	–0.512810
O10...H7	0.114987	0.094988	–0.140642	0.082195	–0.058450
(PC) _{abs}					
C2–O7	0.400878	–0.432266	–1.344134	0.618034	–0.726100
O7...H7	0.026710	0.094978	–0.021659	0.022702	0.001043
O10–H7	0.369537	–2.878148	–0.861265	0.070864	–0.790400
results in ethanol medium					
(RC) _{abs}					
C2–O7	0.294180	–1.112777	–0.364581	0.043193	–0.321390
O7–H7	0.293414	–1.107308	–0.363339	0.043256	–0.320080
O10...H7	0.293414	–1.107098	–0.363449	0.043337	–0.320110
(TS) _{abs}					
C2–O7	0.376976	–0.456285	–1.213806	0.549867	–0.663940
O7...H7	0.186624	–0.683569	–0.339793	0.084450	–0.255340
O10...H7	0.129252	–0.104093	–0.157920	0.065948	–0.091970
(PC) _{abs}					
C2–O7	0.396732	–0.448205	–1.318298	0.603124	–0.715170
O7...H7	0.029673	0.102029	–0.024665	0.025086	0.000421
O10–H7	0.364148	–2.843003	–0.849682	0.069466	–0.780220

^aThe abbreviation RC denotes reactant complex, TS denotes transition state and PC denotes product complex.

^b The symbol ρ denotes electron density (it is measured in $e\text{\AA}^3$), the symbol $\nabla\rho^2$ denotes the Laplacian of the electron density (it is measured in $e\text{\AA}^5$), the symbol V denotes potential energy for the electron at the bond critical point, the symbol G denotes the kinetic energy for the electron at the given bond critical point and H denotes the sum of the potential energy and kinetic energy for the electron at the bond critical point.

The relative energies (calculated with respect to the sum of the energies of the isolated reactant species) are reported in Table 4.5.

Table 4.5: Relative electronic energy (ΔE , kcal/mol), relative enthalpy (ΔH , kcal/mol) and relative Gibbs free energy (ΔG , kcal/mol) for the FG + $\bullet OH$ reaction species related to the DHAA mechanism.

structure ^a	results obtained with the 6-31++G(d,p) basis set			results obtained with the 6-311++G(3df,2p) basis set		
	relative electronic energy (ΔE ,kcal/mol)	relative enthalpy (ΔH ,kcal/mol)	relative free energy (ΔG ,kcal/mol)	relative electronic energy (ΔE ,kcal/mol)	relative enthalpy (ΔE ,kcal/mol)	relative free energy (ΔG ,kcal/mol)
DFT/M06-2X results obtained <i>in vacuo</i>						
(FG + $\bullet OH$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-4.403	-4.315	3.295	-4.192	-4.428	2.443
(TS) _{abs}	-1.295	-1.293	6.464	-0.153	-1.021	8.085
(PC) _{abs}	-32.373	-31.792	-25.457	-32.418	-32.375	-25.865
(P + H ₂ O) _{iso}	-26.002	-25.246	-27.241	-26.750	-26.561	-28.017
DFT/M06-2X results obtained in benzene solvent medium						
(FG + $\bullet OH$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-3.407	-3.324	2.830	-3.124	-3.545	4.358
(TS) _{abs}	0.160	-0.431	7.971	0.816	0.252	8.604
(PC) _{abs}	-31.946	-32.351	-24.815	-31.946	-31.882	-25.553
DFT/M06-2X results obtained in ethanol solvent medium						
(FG + $\bullet OH$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	4.189	3.668	12.346	4.593	4.017	12.678
(TS) _{abs}	-6.519	-7.304	1.576	-5.786	-6.722	2.578
(PC) _{abs}	-32.334	-32.15	-25.772	-32.286	-32.248	-25.642
(P + H ₂ O) _{iso}	-30.184	-29.851	-31.595	-30.333	-30.114	-31.635
DFT/MPW1K results obtained <i>in vacuo</i>						
(FG + $\bullet OH$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-3.687	-3.632	2.651	-3.096	-3.027	3.220
(TS) _{abs}	0.588	-0.041	8.397	1.481	0.855	9.310
(PC) _{abs}	-31.040	-30.856	-25.600	-31.087	-31.029	-24.498
(P + H ₂ O) _{iso}	-26.405	-26.205	-27.670	-27.029	-26.785	-28.333
DFT/MPW1K results obtained in benzene solvent medium						
(FG + $\bullet OH$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-2.615	-2.688	4.256	-2.362	-2.236	3.667
(TS) _{abs}	2.142	1.475	10.071	2.848	2.226	10.734
(PC) _{abs}	-30.887	-31.364	-23.382	-30.879	-30.732	-24.699
(P + H ₂ O) _{iso}	-27.505	-27.330	-28.742	-28.055	-27.816	-29.351
DFT/MPW1K results obtained in ethanol solvent medium						
(FG + $\bullet OH$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-1.645	-1.519	4.836	-0.952	-1.141	6.315
(TS) _{abs}	1.588	0.192	10.658	1.840	0.461	10.732
(PC) _{abs}	-31.207	-31.175	-24.784	-31.055	-31.095	-24.401
(P + H ₂ O) _{iso}	-30.208	-29.885	-31.598	-30.356	-30.081	-31.693
DFT/BHLLYP results obtained <i>in vacuo</i>						
(FG + $\bullet OH$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-3.860	-3.802	2.484	-3.313	-3.223	2.909
(TS) _{abs}	2.965	2.333	10.763	3.872	3.261	11.661
(PC) _{abs}	-31.296	-31.197	-25.069	-31.104	-31.525	-23.839
(P + H ₂ O) _{iso}	-26.086	-25.887	-27.346	-26.628	-26.391	-27.920
DFT/BHLLYP results obtained in benzene solvent medium						
(FG + $\bullet OH$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-2.802	-2.849	4.037	-2.403	-2.380	4.140
(TS) _{abs}	4.373	3.746	12.236	5.168	4.565	12.968
(PC) _{abs}	-30.811	-30.743	-24.325	-30.788	-30.677	-24.756
(P + H ₂ O) _{iso}	-27.319	-27.124	-28.573	-27.727	-27.519	-28.987
DFT/BHLLYP results obtained in ethanol solvent medium						
(FG + $\bullet OH$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-1.882	-1.798	4.692	-1.815	-1.576	4.251
(TS) _{abs}	-2.683	-3.971	6.197	-2.007	-3.293	6.867
(PC) _{abs}	-31.330	-31.762	-23.774	-31.337	-31.737	-24.017
(P + H ₂ O) _{iso}	-30.041	-29.730	-31.416	-30.227	-29.902	-31.608

^aThe abbreviation RC denotes reactant complex, TS denotes transition state and PC denotes product complex.

The results obtained suggest that (RC)_{abs} is more stabilised than the isolated reactant species. The implication of this findings is that the preferred starting geometry for the DHAA mechanism is (RC)_{abs} rather than the isolated reactant species. In other words, FG + •OH proceeds through the formation of the reaction of (RC)_{abs}. The energy of (RC)_{abs} is significantly higher *in vacuo* than in polar medium, suggesting that (RC)_{abs} increases stability with an increase in dielectric constant of a media; the stability is accounted for by the solvent effects [272]. (RC)_{abs} was utilised to locate a minimum energy path scan for the abstraction of H7 atom by O10 atom. Figure 4.3 shows the outcome of the scan; the MEP has three stationary points; two minima and one maximum. The first minimum is located at the O10...H7 bond distance of 1.907 Å while the second minimum is located at O10...H7 bond distance of 0.972 Å. Each individual structure was optimised separately followed by frequency calculations to determine the nature of the stationary points. The outcome of the frequency calculations shows zero imaginary frequencies, indicating that each stationary point is a true minimum on the potential energy surface. The first minimum corresponds to the reactant complex while the second minimum corresponds to the product complex. The structure at the maximum is located at O10...H7 bond distance of 1.335 Å. Optimisation followed by frequency calculation upon the structure obtained at the maximum resulted in one imaginary frequency, implying that it is a transition state structure on the potential energy surface. The imaginary frequency obtained for the O10...H7 bond in the transition state has a magnitude of 1797 cm⁻¹, 2761 cm⁻¹ and 1577 cm⁻¹ *in vacuo*, in benzene and in ethanol, respectively. The IRC analysis, also shown in Figure 4.3, indicates that the obtained transition state structure links the reactant complex and the product complex.

The transition state is denoted as (TS)_{abs}; it is characterised by the elongation of the C7–H7 bond and the shortening of the O10...H7 intermolecular hydrogen bond, as shown in Figure 4.1 and reported in Table 4.3. The O10...H7 bond distance (Å) in (TS)_{abs} is 1.403 *in vacuo*, 1.402 in benzene and 1.336 in ethanol, suggesting that the O10...H7 bond and the O10...H7 bond tends to shorten significantly in polar medium than in non-polar medium. However, the O7–H7 bond distance (Å) is 1.028 *in vacuo*, 1.027 in benzene and 1.240 in ethanol, implying that the O7–H7 covalent bond elongates as the dielectric constant of the media increases.

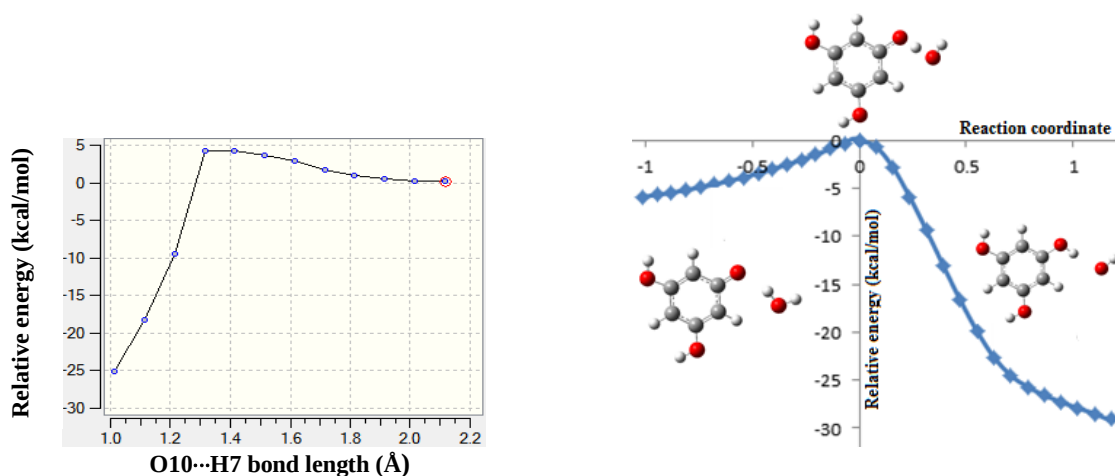


Figure 4.3: O10...H7 bond scan (plot on the left) for FG + •OH for the direct hydrogen atom abstraction of H7, and the corresponding intrinsic reaction coordinate (IRC) plot (plot on the right), starting from the optimised transition state; M06-2X/6-31++G(d,p) results obtained *in vacuo*. The scan was carried out considering steps of 0.1 Å.

Analysis of the molecular graph for (TS)_{abs}, shown in Figure 4.2, suggests that the O7–H7 covalent bond and the O10...H7 intermolecular bond are present in the (TS)_{abs} geometry, a result which is consistent with the analysis of the geometric parameters. The electronic properties at BCP for (TS)_{abs} are reported in Table 4.4. The ρ value for the O7–H7 bond is significantly lower in (TS)_{abs} than in (RC)_{abs} meanwhile the ρ value for the O10...H7 bond increases from (RC)_{abs} to (TS)_{abs}. The implication of these results is that electrons are less accumulated in the region between O7 and H7 atoms in (TS)_{abs} than in (RC)_{abs}. However, electrons are more accumulated in the region between the O10 and H7 atoms in (TS)_{abs} (with an exception of the results obtained in ethanol) than in (RC)_{abs}. No specific trend is observed on the ρ values for the O7–H7 and O10...H7 bond in (TS)_{abs} among different media.

The $\nabla^2\rho$ and H values are all negative for the O7–H7 bond; $\nabla^2\rho$ is positive while H value is negative for the O10...H7 bond, indicating that the O10...H7 bond has both the characters of the strong and weak interactions in nature. Furthermore, a cross comparison of the electronic values for (RC)_{abs} and (TS)_{abs} suggests that the O7–H7 bond weakens

from reactant complex to transition state while the O10...H7 bond strengthens from reactant complex to transition state.

The relative energies for (TS)_{abs}, obtained in all media, are reported in Table 4.5. The energy of (TS)_{abs} is higher than that of (RC)_{abs}; The energy gap between the two structures (i.e., the activation energy (ΔE_{act})) is 4.577 kcal/mol *in vacuo*, 5.210 kcal/mol in benzene and 2.792 kcal/mol in ethanol media, indicating that the reaction barrier height is lower in polar medium than in non-polar medium.

The product complex for the reaction is shown in Figure 4.1 and it is denoted as (PC)_{abs}. The bond distance for the O7...H7 bond is significantly shorter in (TS)_{abs} than in (PC)_{abs} by 0.870 Å *in vacuo*, 0.847 Å in benzene and 0.603 Å in ethanol media, indicating that the O7–H7 covalent bond is broken with respect to (TS)_{abs} and transformed to O7...H7 intermolecular hydrogen bond (in all media) in (PC)_{abs} forming the phenoxyl radical. The O10...H7 bond distance is significantly shorter in (PC)_{abs} than in (TS)_{abs}, indicating that the O10...H7 intermolecular hydrogen bond transforms into the O10–H7 covalent bond, forming the water molecule; it is 0.969 Å *in vacuo*, 0.970 Å in benzene and 0.973 Å in ethanol media, suggesting that there is minimal variation in the O10–H7 covalent bond length obtained in different media.

The molecular graph for (PC)_{abs}, in different media, is shown in Figure 4.2. The results *in vacuo* and in benzene show the existence of two intermolecular bonds; the O7...H7 bond and the O10...H3 bond. These intermolecular bonds are involved in the formation of the ring critical point (five member ring). However, the molecular graph for (PC)_{abs} in ethanol shows only the existence of the O7...H7 intermolecular bond. The existence of the ring critical point in the molecular graph for (PC)_{abs} *in vacuo* and benzene, however, does not result in a more stable structure than in ethanol. This implies that solvent effects contribution to the stability of (PC)_{abs} have greater role to play than the geometric factors.

The electronic properties at BCPs in (PC)_{abs} are reported in Table 4.4. The ρ value for the O7...H7 intermolecular bond is lower in (PC)_{abs} than in (TS)_{abs}, implying that electrons

are less accumulated within the O7...H7 bond in (PC)_{abs} than in the O7–H7 bond present in (TS)_{abs}, which is consistent with the fact that the former bond (i.e., O7...H7 bond) is intermolecular in nature while the latter bond (i.e., O7–H7 bond) is covalent in nature. The $\nabla^2\rho$ and H values for the O7...H7 bond in (PC)_{abs} are all positive, indicating that the O7...H7 bond is a weak bond, characterised as an intermolecular hydrogen bond. The ρ value for the O10–H7 covalent bond is significantly higher in (PC)_{abs} than in the O10...H7 hydrogen bond present in (TS)_{abs}; this result implies that the O10–H7 covalent bond is stronger in (PC)_{abs} than in (TS)_{abs}. The $\nabla^2\rho$ and H values are all negative for the O10–H7 bond in (PC)_{abs}, indicating that the bond formed between the O10 and H7 atoms is covalent in nature.

The relative energy (in different media) for (PC)_{abs} is reported in Table 4.5 and the corresponding energy profile diagram is shown in Figure 4.4 for all the FG + •OH reaction species. The enthalpy of (PC)_{abs} is significantly lower than the enthalpy of (RC)_{abs}, implying that FG + •OH through the DHAA mechanism is exothermic in nature. The change in Gibbs free energies (ΔG) between (PC)_{abs} and (RC)_{abs} is -28.308 kcal/mol *in vacuo*, -29.911 kcal/mol in benzene and -38.321 kcal/mol in ethanol, suggesting that FG + •OH is spontaneous and thermodynamically favoured in all the media. Moreover, the ΔG value is significantly lower in ethanol than *in vacuo* and in benzene; in other words, the reaction is more thermodynamically favoured in polar medium than *in vacuo* or in non-polar medium.

The sum of the energies of the isolated product species (phenoxyl radical and a water molecule) is higher than the energy of (PC)_{abs}, implying that (PC)_{abs} is more stabilised than the isolated product species.

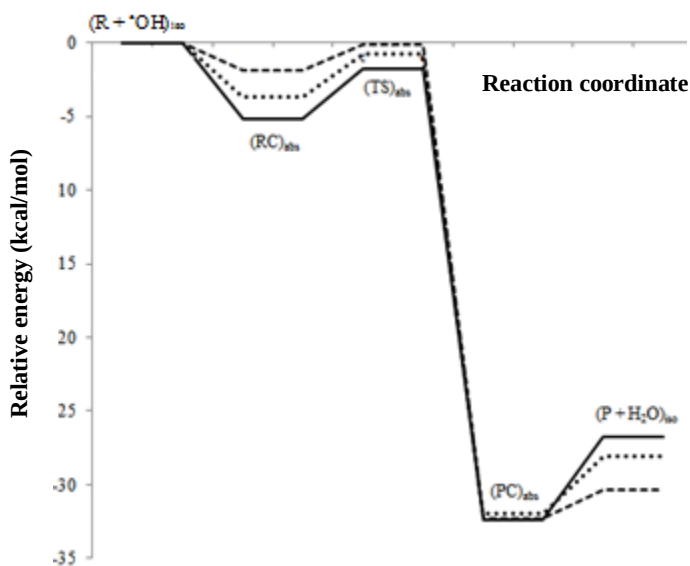


Figure 4.4: M06–2X/6-311++G(3df,2p) energy profile for FG + •OH through the DHAA mechanism, results *in vacuo* (—), in benzene (.....) and in ethanol (-----) media.

The calculated reaction rate constant for FG + •OH, in all media, is denoted throughout the study as k_{abs} and it is reported in Table 4.6; it is of the order of magnitude 10^8 – $10^{10} \text{ M}^{-1}\text{s}^{-1}$, indicating that FG + •OH is diffusion-controlled. However, the k_{abs} results obtained using DFT/BHHLYP are to the order of the magnitude $10^6 \text{ M}^{-1}\text{s}^{-1}$ *in vacuo* and in non-polar medium. A comparison of k_{abs} ($\text{M}^{-1}\text{s}^{-1}$) in different media suggests that it is highest *in vacuo* (8.246×10^{10}) and lowest in benzene (2.555×10^9). The estimated k_{abs} is within the same range as the experimentally determined rate constant for the Phenol + •OH reaction [65, 66, 273].

Table 4.6: Reaction rate constants for the different mechanisms associated with FG + •OH.

calculation method	results obtained using the 6-31++G(d,p) basis set			results obtained using the 6-311++G(3df,2p) basis set		
	<i>in vacuo</i>	in benzene	in ethanol	<i>in vacuo</i>	in benzene	in ethanol
estimated rate constant corresponding to the DHAA mechanism (k_{abs} , $\text{M}^{-1} \text{s}^{-1}$)						
DFT/M06–2X	6.476×10^9	6.193×10^9	4.116×10^9	1.196×10^{11}	2.555×10^9	4.102×10^9
DFT/MPW1K	3.609×10^8	3.128×10^8	3.026×10^8	8.395×10^9	3.869×10^7	2.215×10^9
DFT/BHHLYP	5.023×10^6	5.742×10^6	6.256×10^9	1.041×10^8	1.989×10^6	5.822×10^9
estimated rate constant corresponding to the •OH addition step (k_{add} , $\text{M}^{-1} \text{s}^{-1}$)						
DFT/M06–2X	1.21×10^{11}	1.120×10^{10}	6.253×10^9	8.246×10^{10}	1.137×10^{10}	6.256×10^9
DFT/MPW1K	3.67×10^{10}	1.130×10^{10}	6.244×10^9	2.84×10^{10}	1.023×10^{10}	5.849×10^9
DFT/BHHLYP	5.35×10^7	5.446×10^8	4.933×10^9	1.060×10^7	3.203×10^8	4.993×10^9
estimated rate constant (k_{elim} , s^{-1}) corresponding to the H ₂ O elimination step (in the A-E mechanism) performed without inclusion of the base						
DFT/M06–2X	0.710	2.636	0.276	0.142	0.594	0.105
DFT/MPW1K	0.281	1.357	0.133	0.071	0.338	0.052
DFT/BHHLYP	1.129	6.351	1.404	0.358	2.327	0.518
estimated rate constant ($k_{\text{elim, base}}$, s^{-1}) corresponding to the •OH elimination in the case in which the A-E mechanism is performed with inclusion of the base catalyst ^a						
DFT/BHHLYP	— ^a	2.286×10^6	3.638×10^7	— ^a	8.682×10^5	3.250×10^7
estimated rate constant, k_{oxi} , (s^{-1}) for •H elimination pathway in the case in which oxidation reaction is performed without inclusion of O ₂						
DFT/M06–2X	3.64×10^{-6}	1.43×10^{-6}	3.19×10^{-8}	2.73×10^{-6}	1.08×10^{-6}	4.67×10^{-8}
DFT/MPW1K	3.00×10^{-14}	3.36×10^{-14}	8.25×10^{-14}	5.64×10^{-13}	4.97×10^{-13}	1.87×10^{-12}
DFT/BHHLYP	1.75×10^{-8}	5.02×10^{-9}	1.90×10^{-9}	7.09×10^{-8}	2.56×10^{-8}	7.52×10^{-10}
estimated rate constants for the oxidation reaction for the case in which the mechanism took into consideration inclusion of O ₂ molecule						
estimated rate constant, k_{1,O_2} , (s^{-1}) for the addition of O ₂ to tetrahydroxycyclohexadienyl radical						
DFT/M06–2X	6.98×10^9	6.56×10^2	9.74×10^6	1.77×10^9	1.27×10^3	9.61×10^6
DFT/MPW1K	9.05×10^{-2}	1.15×10^{12}	4.78×10^9	0.122	1.53×10^4	5.76×10^9
DFT/BHHLYP	8.78×10^4	1.36×10^4	3.61×10^8	3.59×10^4	2.39×10^4	2.43×10^8
estimated rate constant, k_{2,O_2} , (s^{-1}) associated with the elimination of the OOH radical						
DFT/M06–2X	6.09×10^6	1.08×10^7	1.27×10^7	9.020×10^6	1.87×10^7	1.95×10^7
DFT/MPW1K	4.21×10^6	1.62×10^7	5.06×10^7	6.089×10^6	2.12×10^7	6.30×10^7
DFT/BHHLYP	4.28×10^5	2.36×10^6	0.100	5.874×10^5	3.20×10^6	6.56×10^7
estimated rate constant, k_{3,O_2} , (s^{-1}) for the isomerisation of trihydroxycyclodienone						
DFT/M06–2X	1.56×10^{-29}	4.40×10^{-30}	2.62×10^{-31}	7.14×10^{-30}	2.09×10^{-30}	2.85×10^{-31}
DFT/MPW1K	4.80×10^{-30}	9.69×10^{-31}	1.77×10^{-32}	3.84×10^{-30}	7.77×10^{-31}	1.34×10^{-32}
DFT/BHHLYP	2.36×10^{-33}	4.60×10^{-34}	2.09×10^{-35}	1.27×10^{-33}	2.99×10^{-34}	9.01×10^{-36}

^a The hydroxyl ion elimination reaction in the presence of a base catalyst was only achieved using the DFT/BHHLYP calculation method. The hydroxyl ion elimination reaction in the presence of a base catalyst can only be envisaged to occur in the presence of solvent molecules. Therefore, the study *in vacuo* has not been performed.

4.3.2 $\bullet$ OH addition step for the A-E and oxidation mechanism

The addition mechanism is thought to proceed through the attachment of $\bullet$ OH at the carbon atom in *ortho* position rather than the *ipso* position. This is because in all the previously studied reactions involving phenol with $\bullet$ OH, the preferred site for phenol + $\bullet$ OH addition reaction has been found to involve the carbon atom in *ortho* position [65, 66]. Also, the only experimental study on FG + $\bullet$ OH has been performed by considering that the addition reaction takes place at the carbon atom in *ortho* position to the phenolic OH [50, 57]. In the study reported in this dissertation, the carbon of interest is C3; $\bullet$ OH was utilised to interact with FG at C3 resulting in the FG... $\bullet$ OH interaction. The optimised reaction species for FG + $\bullet$ OH through the $\bullet$ OH addition are shown in Figure 4.5. The geometric parameters for the optimised reaction species are reported in Table 4.7.

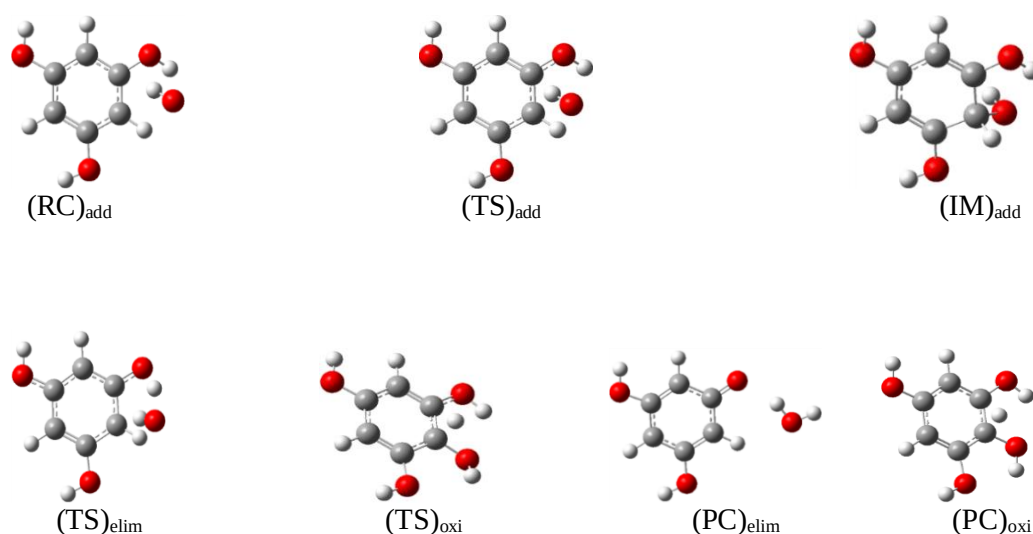


Figure 4.5: M06-2X/6-311++G(3df,2p) optimised FG + $\bullet$ OH reaction species through $\bullet$ OH addition mechanism, water elimination mechanism performed without inclusion of a base catalyst and oxidation mechanism performed without inclusion of O₂. The acronyms “add”, “elim” and “oxi” denote addition, elimination and oxidation, respectively.

Table 4.7: Representative bond lengths (Å), bond angles (°) and torsion angles (°) for the FG + •OH reaction species.

structure ^a and parameters	DFT/M06-2X			DFT/MPW1K			DFT/BHHLYP		
	<i>in vacuo</i>	<i>in benzene</i>	<i>in ethanol</i>	<i>in vacuo</i>	<i>in benzene</i>	<i>in ethanol</i>	<i>in vacuo</i>	<i>in benzene</i>	<i>in ethanol</i>
results obtained while using the 6-31++G(d,p) basis set									
(RC) _{add}									
C2–O7	1.354	1.355	1.359	1.342	1.342	1.346	1.348	1.347	1.352
O7–H7	0.970	0.970	0.969	0.963	0.962	0.959	0.959	0.959	0.959
O10...H7	2.114	2.171	3.442	2.032	2.048	3.367	2.039	2.141	3.408
C3...O10	2.593	2.596	2.593	2.592	2.592	2.592	3.001	2.596	2.596
O7H7O10	130	127	84	136	135	1.079	148	131	90
C1O7H7O10	32	35	49	28	28	89	42	30	47
(TS) _{add}									
C2–O7	1.347	1.348	1.341	1.337	1.338	1.341	1.342	1.343	1.344
O7–H7	0.974	0.972	0.960	0.963	0.963	0.960	0.961	0.960	0.959
O10...H7	2.145	2.190	3.197	2.187	2.260	3.197	2.305	2.409	2.995
C3...O10	2.121	2.196	2.012	2.012	2.033	2.012	1.953	1.962	2.012
O7H7O10	122	121	87	120	118	87	116	113	93
C1O7H7O10	18	22	40	–16	–19	40	15	19	40
(IM) _{add}									
C2–O7	1.355	1.356	1.363	1.346	1.347	1.353	1.351	1.351	1.358
O7–H7	0.969	0.970	0.970	0.960	0.960	0.960	0.958	0.959	0.959
O10...H7	2.254	2.280	2.478	2.238	2.273	2.475	2.280	2.315	2.491
C3–O10	1.440	1.442	1.447	1.427	1.429	1.433	1.432	1.434	1.438
O7H7O10	113	112	105	113	112	105	112	111	105
C1O7H7O10	6	7	16	–6	8	15	5	6	14
results obtained while using the 6-311++G(3df, 2p) basis set									
(RC) _{add}									
C2–O7	1.351	1.351	1.353	1.338	1.338	1.340	1.354	1.342	1.346
O7–H7	0.965	0.965	0.965	0.958	0.958	0.955	0.970	0.955	0.955
O10...H7	2.140	2.224	3.488	2.044	2.113	3.451	2.109	2.190	3.435
C3...O10	2.625	2.613	2.594	2.736	2.592	2.592	2.596	2.596	2.596
O7H7O10	130	125	81	140	132	85	131	130	87
C1O7H7O10	35	38	49	35	32	48	32	33	48
(TS) _{add}									
C2–O7	1.344	1.345	1.335	1.333	1.333	1.335	1.338	1.337	1.338
O7–H7	0.968	0.966	0.955	0.958	0.956	0.955	0.955	0.954	0.955
O10...H7	2.225	2.357	3.118	2.289	2.472	3.118	2.390	2.521	2.979
C3...O10	2.169	2.225	2.012	2.025	2.044	2.012	1.952	1.958	1.997
O7H7O10	119	114	88	117	110	88	113	109	93
C1O7H7O10	22	28	39	–19	–26	39	18	23	37
(IM) _{add}									
C2–O7	1.352	1.352	1.358	1.342	1.342	1.347	1.346	1.347	1.352
O7–H7	0.964	0.965	0.965	0.955	0.955	0.956	0.953	0.953	0.954
O10...H7	2.295	2.319	2.496	2.273	2.302	2.487	2.312	2.340	2.504
C3–O10	1.437	1.438	1.442	1.424	1.425	1.428	1.428	1.430	1.433
O7H7O10	112	111	104	112.0	111	104	111	110	104
C1O7H7O10	8	10	19	8	10	19	7	8	17

^a The abbreviation RC_{add} stands for reactant complex, TS_{add} stands for transition state and IM_{add} stands for intermediate species obtained in the addition mechanism.

The reactant complex is denoted as (RC)_{add}; it has the C3...O10 bond distance (Å) value of 2.625 *in vacuo*, 2.613 in benzene and 2.594 in ethanol media, suggesting that the C3...O10 bond distance decreases with the increase in dielectric constant of the media. The C2–O7–H7–O10 torsion angle is within a range of 35°–48°, indicating that it is significantly off plane. The corresponding molecular graphs for the optimised species are presented in Figure 4.6. The results obtained show that (RC)_{add} has two intermolecular bonds; the O10...H7 bond and the C3...O10 bond. These intermolecular bonds contribute to the formation of a five member ring, which is confirmed by the existence of a ring critical point.

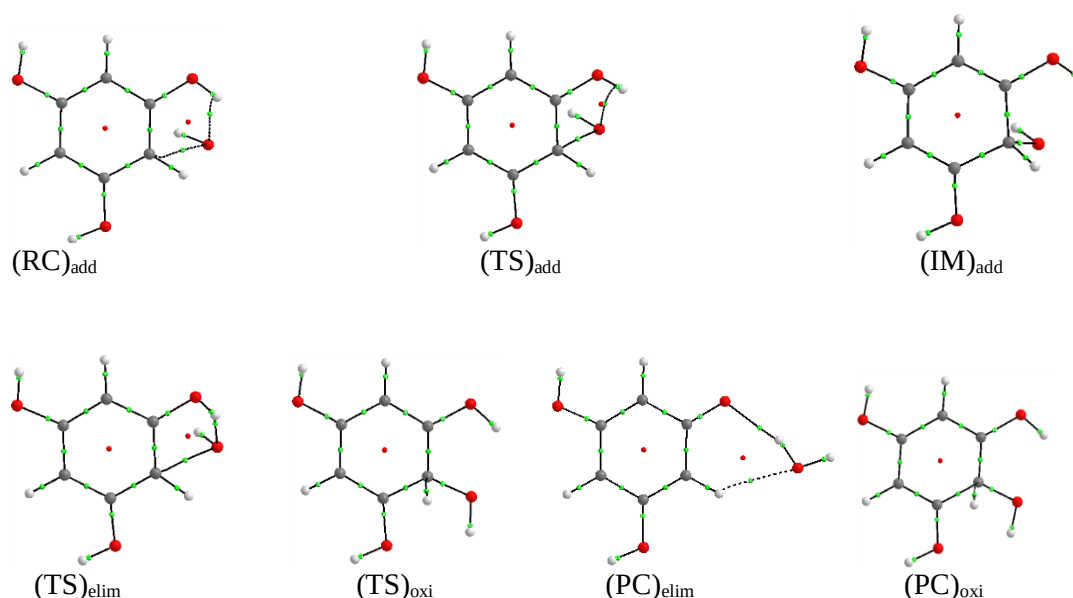


Figure 4.6: Molecular graphs for the of the FG + $\bullet\text{OH}$ reaction species involved in the $\bullet\text{OH}$ addition mechanism, water elimination mechanism performed without inclusion of a base catalyst and oxidation mechanism without inclusion of O_2 . The acronym “add”, “elim” and “oxi” stands for addition, elimination and oxidation, respectively. The green dot within a given bond represents the bond critical point while the red dot within a given ring stands for the ring critical point.

The electronic properties at BCPs for the reaction species are reported in Table 4.8. The $\nabla^2\rho$ and H values for the C3...O10 bond are all positive, implying that the C3...O10 intermolecular bond is weak in nature. The relative energies for the reaction species are reported in Table 4.9.

Table 4.8: Bond critical point properties for selected bonds within the FG + •OH reaction species obtained through the A-E mechanism that was performed without inclusion of a base catalyst and oxidation mechanism that was performed without inclusion of the O₂ molecule.

structure ^a and bond type	electron density ρ (eÅ ³)	Laplacian of the electron density $\nabla\rho^2$ (eÅ ⁵)	potential electron energy density V (Hartree)	kinetic electron energy density G (Hartree)	total electron energy density H (Hartree)
BHHLYP/6-311++G(3df,2p) results obtained <i>in vacuo</i>					
(RC) _{add}					
C2-O7	0.299912	-0.524398	-0.783151	0.326026	-0.457130
O7-H7	0.363573	-2.774324	-0.828611	0.067515	-0.761100
O10...H7	0.018242	0.069497	-0.014316	0.015845	0.001529
C3...O10	0.019021	0.069968	-0.013534	0.015513	0.001979
(TS1) _{add}					
C2-O7	0.315161	-0.563938	-0.875620	0.367317	-0.508300
O7-H7	0.378283	-2.985099	-0.882354	0.068039	-0.814320
C3...O10	0.079380	0.147144	-0.067195	0.051991	-0.015200
C3...H3	0.302587	-1.183457	-0.373096	0.038616	-0.334480
(IM) _{add}					
C1-O7	0.304862	-0.460029	-0.853765	0.369379	-0.484390
O7-H7	0.381510	-2.993812	-0.889076	0.070312	-0.818760
C3-O10	0.384847	-2.953191	-0.890677	0.076190	-0.814490
C3-H3	0.293529	-1.104825	-0.350665	0.037230	-0.313440
(TS) _{elim}					
C2-O7	0.323745	-0.772367	-0.833727	0.320318	-0.513410
O7...H7	0.207068	-0.643677	-0.373334	0.106207	-0.267130
O10...H7	0.177640	-0.272631	-0.325959	0.128900	-0.197060
C3-O10	0.219010	-0.372713	-0.455687	0.181254	-0.274430
(TS) _{oxi}					
C2-O7	0.314555	-0.515778	-0.884549	0.377802	-0.506750
O7-H7	0.380086	-3.001239	-0.887082	0.068386	-0.818700
C3...O10	0.294576	-0.532238	-0.780609	0.323775	-0.456830
C3...H3	0.056277	0.036140	-0.034437	0.021736	-0.012700
(PC) _{elim}					
C2-O7	0.401583	-0.433655	-1.347491	0.619539	-0.727950
O7...H7	0.026229	0.093306	-0.021300	0.022313	0.001013
O10-H7	0.370890	-2.889357	-0.864786	0.071223	-0.793560
O10...H3	0.007577	0.031199	-0.005195	0.006497	0.001302
(PC) _{oxi}					
C2-O7	0.308740	-0.523082	-0.854090	0.361660	-0.492430
O7...H7	0.381919	-3.006508	-0.890557	0.069465	-0.821090
C3-O10	0.293433	-0.441850	-0.801033	0.345285	-0.455750
C3...H3	0.004865	0.011269	-0.002290	0.002554	0.000264
BHHLYP/6-311++G(3df,2p) results obtained in benzene solvent medium					
(RC) _{add}					
C2-O7	0.311084	-0.564339	-0.855739	0.357327	-0.498400
O7-H7	0.378921	-2.992394	-0.885141	0.068521	-0.816600
C3...O10	0.015869	0.060838	-0.012056	0.013633	0.001580
C3-H3	0.296137	-1.127536	-0.368074	0.043095	-0.325000
(TS) _{add}					
C2-O7	0.314111	-0.536395	-0.878591	0.372246	-0.506300
O7-H7	0.379254	-2.993496	-0.884182	0.067904	-0.816300
C3...O10	0.078477	0.145425	-0.065803	0.051080	-0.014700

C3-H3	0.302183	-1.180878	-0.371872	0.038326	-0.333500
(IM) _{add}					
C2-O7	0.304164	-0.448649	-0.853772	0.370805	-0.483000
O7-H7	0.380696	-2.990422	-0.887101	0.069748	-0.817400
C3-O10	0.255901	-0.567629	-0.561282	0.209687	-0.351600
C3-H3	0.293958	-1.108402	-0.350837	0.036868	-0.314000
(TS) _{elim}					
C2-O7	0.321163	-0.757720	-0.826101	0.318336	-0.507800
O7-H7	0.206406	-0.637864	-0.372970	0.106752	-0.266200
O10-H7	0.178060	-0.280723	-0.326627	0.128223	-0.198400
C3-O10	0.219015	-0.372526	-0.455966	0.181417	-0.274500
(TS) _{oxi}					
C2-O7	0.314144	-0.507723	-0.884958	0.379013	-0.505900
O7-H7	0.379076	-2.995960	-0.884742	0.067876	-0.816900
C3-O10	0.295753	-0.526849	-0.788011	0.328149	-0.459900
C3-H3	0.055408	0.037580	-0.033708	0.021551	-0.012200
(PC) _{elim}					
C2-O7	0.400874	-0.432346	-1.344091	0.618002	-0.726100
O7-H7	0.026690	0.094895	-0.021636	0.022680	0.001040
O10-H7	0.369552	-2.878252	-0.861297	0.070867	-0.790400
(PC) _{oxi}					
C2-O7	0.308078	-0.512812	-0.853966	0.362881	-0.491100
O7-H7	0.380921	-3.001514	-0.888267	0.068944	-0.819300
C3-O10	0.294345	-0.437614	-0.806584	0.348590	-0.458000
C3-H3	0.004474	0.010000	-0.001986	0.002243	0.000260
BHLYP/6-311++G(3df,2p) results obtained in ethanol solvent medium					
(RC) _{add}					
C2-O7	0.306783	-0.522895	-0.847055	0.358166	-0.488900
O7-H7	0.377907	-3.009938	-0.883465	0.065490	-0.818000
C3-O10	0.019872	0.062843	-0.012700	0.014206	0.001510
C3-H3	0.295460	-1.125261	-0.365123	0.041904	-0.323200
(TS) _{add}					
C2-O7	0.311812	-0.507261	-0.875568	0.374376	-0.501200
O7-H7	0.376293	-3.006984	-0.880463	0.064359	-0.816100
C3-O10	0.072469	0.140128	-0.058478	0.046755	-0.011700
C3-H3	0.302179	-1.184139	-0.370460	0.037212	-0.333200
(IM) _{add}					
C2-O7	0.293460	-1.111573	-0.361366	0.041736	-0.319600
O7-H7	0.295506	-1.121370	-0.352542	0.036100	-0.316400
C3-O10	0.279501	-0.768475	-0.316998	0.062440	-0.254600
C3-H3	0.296977	-0.436878	-0.822816	0.356798	-0.466000
(TS) _{elim}					
C2-O7	0.306259	-0.728602	-0.757649	0.287749	-0.469900
O7-H7	0.204170	-0.620258	-0.371337	0.108136	-0.263200
O10-H7	0.179425	-0.308923	-0.328770	0.125770	-0.203000
C3-O10	0.220039	-0.386641	-0.454065	0.178702	-0.275400
(TS) _{oxi}					
C2-O7	0.310669	-0.509823	-0.867588	0.370066	-0.497500
O7-H7	0.374427	-2.988914	-0.876693	0.064732	-0.812000
C3-O10	0.294446	-0.541404	-0.776919	0.320784	-0.456100
C3-H3	0.053506	0.040182	-0.032148	0.021097	-0.011100
(PC) _{elim}					
C2-O7	0.396702	-0.450081	-1.317685	0.602582	-0.715100
O7-H7	0.029499	0.100805	-0.024422	0.024812	0.000390
O10-H7	0.364223	-2.842889	-0.849742	0.069510	-0.780200
(PC) _{oxi}					
C2-O7	0.303306	-0.509530	-0.831859	0.352238	-0.479600
O7-H7	0.376580	-2.998476	-0.881148	0.065765	-0.815400
C3-O10	0.293655	-0.455799	-0.797862	0.341956	-0.455900
C3-H3	0.004705	0.010759	-0.002189	0.002440	0.000250

^aThe abbreviation (RC)_{add} stands for reactant complex species, (TS)_{add} stands for transition state, (IM)_{add} stands for intermediate and (PC)_{add} stands for product species. The abbreviations “elim” and “oxi” in TS and PC denote TS and PC structures obtained through the A-E mechanism and oxidation mechanism, respectively.

Table 4.9: Relative electronic energy (ΔE , kcal/mol), relative enthalpy (ΔH , kcal/mol) and relative Gibbs free energy (ΔG , kcal/mol) for the FG + $\bullet\text{OH}$ reaction species related to the first step of the A-E mechanism, the second step of A-E mechanism when performed without addition of a catalyst and reaction species corresponding to oxidation mechanism performed without addition of O_2 .

structure ^a	results obtained using the 6-31++G(d,p) basis set			results obtained using the 6-311++G(3df,2p) basis set		
	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative free energy (ΔG , kcal/mol)	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative free energy (ΔG , kcal/mol)
DFT/M06-2X results <i>in vacuo</i>						
(R+ $\bullet\text{OH}$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{add}	-5.649	-5.482	2.132	-5.207	-5.525	2.623
(TS) _{add}	-4.368	-4.828	4.433	-4.007	-4.950	4.600
(IM) _{add}	-20.367	-20.875	-11.455	-20.272	-21.304	-11.427
(TS) _{elim}	-2.759	-3.455	6.168	-1.736	-2.996	7.149
(TS) _{oxi}	4.189	3.742	13.385	4.441	3.447	13.585
(PC) _{elim}	-32.374	-31.792	-25.464	-32.438	-32.380	-25.997
(P) _{oxi}	0.056	0.023	8.808	0.132	-0.585	9.025
(P+H ₂ O) _{iso}	-26.002	-25.246	-27.241	-26.750	-26.561	-28.017
(P+ $\bullet\text{H}$) _{iso}	-1.303	-0.446	1.693	-1.019	-0.777	2.010
DFT/M06-2X results in benzene solvent medium						
(R+ $\bullet\text{OH}$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{add}	-3.919	-4.231	3.724	-3.620	-3.876	3.909
(TS) _{add}	-3.124	-4.019	5.432	-2.985	-3.719	5.139
(IM) _{add}	-18.377	-19.444	-9.497	-18.436	-19.463	-9.582
(TS) _{elim}	-1.571	-2.847	7.349	-0.759	-2.012	8.147
(TS) _{oxi}	6.833	5.887	15.894	6.873	5.925	15.978
(PC) _{elim}	-32.030	-32.402	-25.105	-32.052	-31.952	-25.751
(P) _{oxi}	3.040	2.443	11.822	2.8558	2.172	11.753
(P+H ₂ O) _{iso}	-27.266	-27.105	-28.503	-28.046	-27.849	-29.310
(P+ $\bullet\text{H}$) _{iso}	1.579	1.886	4.543	1.608	1.888	4.612
DFT/M06-2X results in ethanol solvent medium						
(R+ $\bullet\text{OH}$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{add}	-4.198	-4.019	2.388	-4.046	-4.132	3.165
(TS) _{add}	-4.232	-4.835	3.909	-4.126	-5.188	4.667
(IM) _{add}	-18.717	-19.431	-10.146	-18.658	-19.503	-9.962
(TS) _{elim}	-0.903	-2.095	8.036	-0.218	-1.505	8.791
(TS) _{oxi}	8.474	7.607	17.500	8.323	7.354	17.459
(PC) _{elim}	-31.917	-31.876	-25.063	-31.930	-32.022	-24.991
(P) _{oxi}	5.114	4.630	13.763	4.707	4.043	13.560
(P+H ₂ O) _{iso}	-30.184	-29.851	-31.595	-30.333	-30.114	-31.635
(P+ $\bullet\text{H}$) _{iso}	2.934	13.414	5.747	1.327	1.625	4.320
DFT/MPW1K results <i>in vacuo</i>						
(R+ $\bullet\text{OH}$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{add}	-3.096	-3.470	4.427	-2.646	-2.868	4.480
(TS) _{add}	-1.357	-2.399	7.436	-0.993	-1.943	7.639
(IM) _{add}	-17.484	-18.500	-8.683	-17.355	-18.336	-8.580
(TS) _{elim}	0.704	-6.806	9.489	1.638	0.455	10.409
(TS) _{oxi}	17.826	16.516	27.184	16.238	3.296	12.246
(PC) _{elim}	-31.287	-31.249	-24.600	-31.087	-31.029	-24.504
(P) _{oxi}	6.492	6.493	14.236	5.600	5.513	13.272
(P+H ₂ O) _{iso}	-26.405	-26.205	-27.669	-27.029	-26.785	-28.333
(P+ $\bullet\text{H}$) _{iso}	3.674	3.950	7.651	2.929	3.196	3.922
DFT/MPW1K results in benzene solvent medium						
(R+ $\bullet\text{OH}$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{add}	-1.258	-2.147	7.361	-0.780	-0.996	6.152
(TS) _{add}	0.107	-0.851	8.717	0.200	-0.627	8.634
(IM) _{add}	-15.426	-16.442	-6.609	-15.506	-16.468	-6.708
(TS) _{elim}	1.837	0.628	10.631	2.579	1.413	11.355
(TS) _{oxi}	19.818	18.504	29.192	19.429	17.742	28.861
(PC) _{elim}	-32.678	-32.795	-36.130	-30.766	-30.817	-34.334
(P) _{oxi}	9.558	9.552	17.450	8.369	8.394	16.032
(P+H ₂ O) _{iso}	-27.505	-27.330	-28.742	-28.055	-27.816	-29.351
(P+ $\bullet\text{H}$) _{iso}	7.597	7.887	10.568	6.593	6.899	9.557
DFT/MPW1K results in ethanol solvent medium						

(R+•OH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{add}	-1.367	-1.769	6.106	-1.110	-1.173	5.526
(TS) _{add}	-0.990	-2.026	7.685	-0.776	-1.933	8.107
(IM) _{add}	-15.638	-16.343	-7.098	-15.729	-16.527	-7.081
(TS) _{elim}	2.567	1.500	11.519	3.178	1.969	12.088
(TS) _{oxi}	18.819	17.514	28.170	16.976	15.725	26.339
(P) _{oxi}	11.641	11.300	19.952	10.363	10.306	18.360
(P+H ₂ O) _{iso}	-30.208	-29.885	-31.598	-30.356	-30.081	-31.693
(P+•H) _{iso}	10.088	10.445	13.020	8.907	8.928	12.174
DFT/BHLLYP results in vacuo						
(R+•OH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{add}	-3.313	-3.437	3.364	-3.326	-3.222	2.823
(TS) _{add}	1.461	0.449	10.242	1.952	1.000	10.658
(IM) _{add}	-12.931	-13.920	-4.137	-12.578	-13.530	-3.809
(TS) _{elim}	4.499	3.346	13.212	5.548	4.428	14.219
(TS) _{oxi}	14.713	13.707	23.866	16.265	13.296	23.365
(PC) _{elim}	-31.291	-31.197	-24.996	-31.104	-31.524	-23.838
(P) _{oxi}	10.181	10.500	16.728	9.629	9.853	16.640
(P+H ₂ O) _{iso}	-26.086	-25.890	-27.346	-26.628	-26.391	-27.920
(P+•H) _{iso}	10.054	10.327	13.035	9.480	9.739	12.172
DFT/BHLLYP results in benzene solvent medium						
(R+•OH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{add}	-0.862	-1.117	5.896	-0.372	-0.553	5.892
(TS) _{add}	2.718	1.800	11.370	3.085	2.199	11.692
(IM) _{add}	-11.002	-11.977	-2.197	-10.737	-11.706	-1.907
(TS) _{elim}	5.365	4.208	14.128	6.308	5.179	15.013
(TS) _{oxi}	17.418	16.436	26.546	16.781	15.819	25.869
(PC) _{elim}	-30.911	-31.339	-23.675	-30.792	-30.677	-24.782
(P) _{oxi}	13.214	13.477	20.243	12.501	12.661	20.005
(P+H ₂ O) _{iso}	-27.319	-27.124	-28.573	-27.727	-27.519	-28.987
(P+•H) _{iso}	8.950	8.687	12.413	9.149	8.917	12.581
DFT/BHLLYP results in ethanol solvent medium						
(R+•OH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{add}	-0.926	-0.795	5.713	-0.820	-0.744	5.958
(TS) _{add}	0.583	-0.104	9.019	0.771	0.061	9.231
(IM) _{add}	-11.360	-12.063	-2.810	-11.314	-12.010	-2.777
(TS) _{elim}	5.605	7.620	14.409	6.233	5.159	15.033
(TS) _{oxi}	18.950	18.124	27.873	18.022	17.114	27.090
(PC) _{elim}	-31.342	-31.267	-24.955	-31.271	-31.184	-25.428
(P) _{oxi}	15.690	16.027	22.600	14.476	14.713	21.679
(P+H ₂ O) _{iso}	-30.041	-29.730	-31.416	-30.227	-29.902	-31.608
(P+•H) _{iso}	19.794	19.863	22.864	18.453	18.511	21.511

^aThe abbreviation RC_{add} denotes reactant complex, TS denotes transition state, IM denotes intermediate species, PC_{add} denotes product complex species and P_{iso} denotes isolated product species. The abbreviation “elim” in TS and PC stands for second transition state and product complex obtained through the A-E mechanism and “oxi” in TS and PC denotes the second transition state and product obtained through the oxidation mechanism.

The total energy of the separate reactant species is higher than that of (RC)_{add}, implying that (RC)_{add} is more stable than the isolated reactant species; therefore, the preferred starting structure for the addition mechanism is (RC)_{add} rather than the separated reactant species. The energy of (RC)_{add} is lowest in ethanol medium and highest *in vacuo*, implying that the energy of (RC)_{add} decreases with an increase in dielectric constant of the media.

The MEP scan for the C3...O10 intermolecular bond in (RC)_{add} and the IRC scan for the addition of •OH to the FG moiety are shown in Figure 4.7. The potential surface possesses

two minima points and one maximum point. The minimum point found to the left of the maximum point is located at C3...O10 bond distance of 2.593 Å while the minimum point

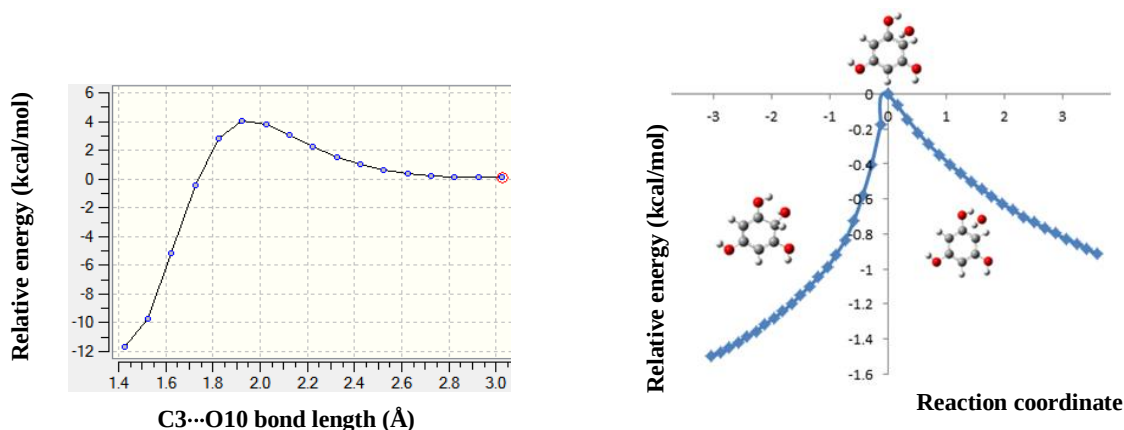


Figure 4.7: BHHLYP/6-31+G(d,p) result on the scan (in steps of 0.1 Å) for the C3...O10 bond (left) corresponding to FG + •OH, resulting in the attachment of •OH on the ring at C3, and the corresponding plot (right) for the intrinsic reaction coordinate starting from the optimised transition state obtained in the •OH addition.

to the right of the maximum point is located at C3...O10 bond distance of 1.493 Å. Optimisation followed by frequency calculations upon the structure at the first minimum and the structure at the second minimum gave zero imaginary frequency. The first minimum corresponds to the reactant complex while the second minimum corresponds to the intermediate species. The structure at the maximum is located at the C3...O10 bond distance of 2.093 Å. Optimisation followed by frequency calculation upon the structure at the maximum resulted in one imaginary frequency, implying that it is a transition state on the potential energy surface. The magnitude of the imaginary frequency (cm^{-1}) of the found transition state is 390 *in vacuo*, 191 in benzene and 251 in ethanol media. The IRC analysis indicates that the transition state joins the reactant complex species and the intermediate species.

The transition state for the •OH addition step is denoted as (TS)_{add}; it is characterised by the shortening of the C3...O10 intermolecular bond distance with respect to the value it has in (RC)_{add}, as reported in Table 4.7. The molecular graph (Figure 4.6) shows the

existence of the C3...O10 intermolecular bond in (TS)_{add} (which is consistent with the analysis for the geometric findings) which forms part of the five member ring, identifiable by the existence of ring critical point.

The ρ value for the C3...O10 bond is higher in (TS)_{add} than in (RC)_{add}, implying that electrons are more accumulated within the C3...O10 bond in the transition state structure than in the reactant complex structure. The $\nabla^2\rho$ value is positive and the H value is negative for the C3...O10 bond in (TS)_{add}, which implies that the C3...O10 bond has both the weak and strong interaction characters in nature.

The intermediate species, which results from the addition of •OH onto the phloroglucinol moiety, is a tetrahydroxycyclohexadienyl radical; it is denoted as (IM)_{add}; it is characterised by the existence of the C3–O10 covalent bond. The C3–O10 bond has a length (Å) of 1.437 in *vacuum* medium, 1.438 in benzene solvent medium and 1.442 in ethanol solvent medium. The molecular graph for (IM)_{add} (Figure 4.6) shows the existence of the C3–O10 bond. The ρ value for the C3–O10 bond in (IM)_{add} is higher than for the C3...O10 bond in (TS)_{add}, implying that there is high electron density within the C3–O10 bond in (IM)_{add} than within the C3...O10 bond in (TS)_{add}. The $\nabla^2\rho$ and H values are positive, indicating that the C3–O10 bond present in (IM)_{add} is covalent in nature.

(RC)_{add} has higher enthalpy than (IM)_{add}, implying that FG + •OH through •OH addition step is exothermic in nature. The ΔE_{act} value decreases with an increase in dielectric constant of the media, suggesting that if we consider a biological system, then the reaction barrier height is lower in polar solvent than in non-polar solvent. The implication of this result is that the reactivity of FG towards •OH is far enhanced in polar solvent with respect to non-polar one. ΔE_{act} values are lower for the •OH addition step than for the DHAA mechanism. Therefore, it is reasonable to infer that the •OH addition step is likely to occur quicker than the DHAA mechanism.

The estimated rate constant for the addition step is denoted as k_{add} ; its values in different media are reported in Table 4.6. The k_{add} value suggests the preference of the FG + •OH reaction as a diffusion-controlled type of a reaction. The results obtained are consistent

with the available experimental data for FG + •OH as well as phenol + •OH [65, 66], which shows that the rate constant for the reaction of phenolic derivatives with •OH are diffusion controlled.

The k_{add} value (for the •OH addition step) is significantly higher than the k_{abs} value (for the DHAA mechanism), suggesting that the FG + •OH reaction is faster through the •OH addition step than through the DHAA pathway. In other words, the •OH addition mechanism is kinetically preferred to the DHAA mechanism. The findings reported here are also in agreement with the experimental results on FG + •OH as well as phenol + •OH [50, 57, 273], where it is reported that the •OH addition step is kinetically preferred to the direct hydrogen atom transfer pathway.

The calculated branching ratios for the product species obtained in the addition step (i.e., tetrahydroxycyclohexadienyl radical) and in the DHAA mechanism (i.e., phenoxyl radical) are reported in Table 4.10; the branching ratios are obtained by utilising the calculated rate constants for the DHAA mechanism and for the •OH addition step, as reported in Table 4.6. The estimated branching ratios for the DHAA mechanism and for the •OH addition step are denoted as Γ_{abs} and Γ_{add} , respectively. The Γ_{abs} values are significantly lower than the Γ_{add} values, indicating that the tetrahydroxycyclohexadienyl radical is more likely to form than the phenoxyl radical. The results are in agreement with the estimated rate constants as well as the experimental findings [50, 57].

Table 4.10: Estimated branching ratio (Γ (%)), in different media and with different methods, for FG + •OH through the DHAA mechanism and the •OH addition step in the A-E mechanism, respectively.

calculation method	Γ_{abs}^a	Γ_{add}^a	Γ_{abs}	Γ_{add}
	<i>in vacuo</i> results with the 6-31++G(d,p) basis set		<i>in vacuo</i> results with the 6-311++G(3df,2p) basis set	
DFT/M06-2X	5.076	94.924	0.030	99.970
DFT/MPW1K	0.975	99.025	22.791	77.209
DFT/ BHHLYP	8.581	91.419	9.256	90.744
	results in benzene with the 6-31++G(d,p) basis set		results in benzene with the 6-311++G(3df,2p) basis set	
DFT/M06-2X	35.689	64.311	18.346	81.654
DFT/MPW1K	2.687	97.313	0.377	99.623
DFT/ BHHLYP	1.043	98.957	0.617	99.383
	results in ethanol with the 6-31++G(d,p) basis set		results in ethanol with the 6-311++G(3df,2p) basis set	
DFT/M06-2X	1.496	98.504	0.668	99.332
DFT/MPW1K	4.623	95.377	27.471	72.529
DFT/ BHHLYP	55.909	44.091	53.836	46.164

^aThe symbol Γ_{abs} stands for the branching ratio for the reaction through the DHAA mechanism and Γ_{add} denotes the branching ratio for the species obtained from the •OH addition step in the A-E mechanism.

Overall, the findings on $\text{FG} + \bullet\text{OH}$ through DHAA mechanism and addition mechanism suggest that there is high preference for the occurrence of $\text{FG} + \bullet\text{OH}$ through the addition mechanism than DHAA mechanism. As a consequence, the subsequent subsections proceed to discuss the results of the outcome of the investigation on the conversion of the intermediate species, obtained in the addition step, to product species, through the dehydration mechanism and the O_2 oxidation mechanism.

4.3.3 Dehydration step performed without inclusion and with inclusion of the base (OH^-) as a catalyst

The intermediate, tetrahydroxycyclohexadienyl radical, obtained in the addition step can be converted into phenoxyl radical species through removal of a water molecule. During the water removal, the H7 atom, which in the intermediate is attached to O7, is transferred to O10, leading to the formation of the phenoxyl radical and a water molecule as product species; this investigation has been performed in a neutral environment and in a basic environment. The study was performed in a basic environment in order to improve the rate of the reaction; it has been reported that the dehydration step for the phenol(s) + $\bullet\text{OH}$ reaction is too slow to occur under neutral conditions and that the performance of the reaction under either basic or acidic medium helps to speed up the reaction [50, 57, 273].

4.3.3.1 Dehydration step performed without inclusion of the base

The optimised structures of the reaction species for the water removal step, starting from $(\text{IM})_{\text{add}}$, in the absence of the base are identified by a superscript “elim” and are presented in Figure 4.5; they are the transition state structure, $(\text{TS})_{\text{elim}}$, and the product structure, $(\text{PC})_{\text{elim}}$. The geometric properties for these reaction species are reported in Table 4.11. $(\text{TS})_{\text{elim}}$ and $(\text{PC})_{\text{elim}}$ were obtained by running the $\text{O10}\cdots\text{H7}$ bond scan starting from $(\text{IM})_{\text{add}}$; the scan is shown in Figure 4.8.

The MEP scan is characterised by the presence of two minima points and one maximum point. The first minimum and the second minimum points are located at the $\text{O10}\cdots\text{H7}$ bond distance of 2.254 Å and 0.953 Å, respectively. The outcome of optimisation followed by the frequency calculations on the individual structures at each minimum point suggests that they each have zero imaginary frequency, indicating that they are

Table 4.11: Representative bond lengths (Å), bond angles (°) and torsion angles (°)) for the FG + •OH reaction species obtained through the dehydration step performed without addition of a base catalyst and the oxidation mechanism performed without inclusion of the O₂ molecule.

structure ^a and parameters	DFT/M06-2X			DFT/MPW1K			DFT/BHLLYP		
	<i>in vacuo</i>	<i>in benzene</i>	<i>in ethanol</i>	<i>in vacuo</i>	<i>in benzene</i>	<i>in ethanol</i>	<i>in vacuo</i>	<i>in benzene</i>	<i>in ethanol</i>
results obtained using 6-31++G(d, p) basis set for the dehydration step performed without inclusion of the base									
(TS) _{elim} ^b									
C2–O7	1.350	1.352	1.372	1.343	1.345	1.364	1.348	1.351	1.371
O7...H7	1.160	1.160	1.160	1.160	1.160	1.160	1.160	1.160	1.160
O10...H7	1.171	1.171	1.171	1.171	1.171	1.171	1.171	1.171	1.171
C3–O10	1.485	1.485	1.485	1.485	1.485	1.485	1.485	1.485	1.485
O7H7O10	180	180	180	180	180	180	180	180	180
C3C2O10H10	92	92	93	92	92	92	92	92	92
C4C3C2H2	–104	–104	–104	–104	–104	–104	–104	–104	–104
(PC) _{elim}									
C1–O7	1.254	1.255	1.259	1.247	1.246	1.251	1.248	1.248	1.251
O7...H7	1.906	1.883	1.847	1.888	1.882	1.843	1.909	1.888	1.857
O10–H7	0.972	0.973	0.976	0.964	0.964	0.968	0.963	0.964	0.967
O7H7O10	156	162	176	161	180	180	160	173	179
C1O7H7O10	0	0	3	2	91	97	0	1	14
results obtained using the 6-311++G(3df, 2p) basis set for the dehydration step performed without inclusion of the base									
(TS) _{elim}									
C2–O7	1.345	1.303	1.365	1.336	1.339	1.356	1.341	1.344	1.363
O7...H7	1.160	1.091	1.160	1.160	1.160	1.160	1.160	1.160	1.160
O10...H7	1.171	1.370	1.171	1.171	1.171	1.171	1.171	1.171	1.171
C3–O10	1.485	1.485	1.486	1.485	1.485	1.485	1.486	1.485	1.485
O7H7O10	180	180	180	180	180	180	180	180	180
C3C2O10H10	92	92	93	92	92	92	92	92	92
C4C3C2H2	–104	–104	–104	–104	–104	–104	–104	–104	–104
(PC) _{elim}									
C1–O7	1.243	1.245	1.250	1.237	1.237	1.242	1.237	1.237	1.241
O7...H7	1.898	1.874	1.841	1.894	1.888	1.843	1.912	1.895	1.856
O10–H7	0.969	0.970	0.972	0.961	0.961	0.965	0.959	0.960	0.963
O7H7O10	160	167	176	165	180	180	163	174	179
C1O7H7O10	0	0	1	2	90	61	0	2	14
results obtained using the 6-31++G(d, p) basis set for the oxidation step performed without inclusion of the O ₂ molecule									
(TS) _{oxi} ^b									
C2–O7	1.347	1.347	1.353	1.361	1.359	1.357	1.341	1.341	1.345
O7–H7	0.969	0.970	0.972	0.960	0.961	0.962	0.959	0.959	0.961
C3...H3	1.797	2.389	1.822	1.797	1.797	1.796	1.836	1.846	1.872
O7H7O10	114	114	112	82	82	98	113	113	112
C4C3C2H2	91	91	91	91	91	90	91	91	91
C3C2O10H10	–43	–42	–58	142	143	155	–41	–43	–58
(PC) _{oxi}									
C1–O7	1.354	1.354	1.361	1.343	1.343	1.350	1.348	1.348	1.355
O7–H7	0.968	0.969	0.970	0.959	0.959	0.961	0.957	0.958	0.960
C3...H3	2.394	2.394	2.394	2.394	2.394	2.394	3.082	3.282	3.081
C2–H3	2.657	2.649	2.649	2.775	2.752	2.769	3.370	3.556	3.367
O7H7O10	113	113	111	113	113	111	113	112	110
C4C3C2H2	79	79	79	89	87	89	89	89	89
results obtained using the 6-311++G(3df, 2p) basis set for the oxidation step performed without inclusion of the O ₂ molecule									
(TS) _{oxi}									

C2–O7	1.343	1.343	1.348	1.357	1.355	1.359	1.336	1.336	1.341
O7–H7	0.965	0.966	0.968	0.956	0.957	0.958	0.954	0.954	0.957
C3···H3	1.772	1.785	1.795	1.797	1.797	1.797	1.806	1.813	1.831
O7H7O10	114	113	112	78	101	93	113	112	111
C4C3C2H2	91	91	90	90	89	88	91	91	90
C3C2O10H10	–42	–41	–48	150	151	171	–43	–41	–50
(PC) _{oxi}									
C1–O7	1.350	1.350	1.356	1.339	1.339	1.344	1.344	1.343	1.350
O7–H7	0.964	0.965	0.966	0.956	0.955	3.377	0.953	0.954	0.955
C3···H3	2.394	2.394	2.394	2.394	2.394	2.394	3.160	3.192	3.188
C2–H3	2.614	2.615	2.619	2.719	2.709	2.708	3.226	3.323	3.256
O7H7O10	113	113	111	113	78	111	113	112	110
C4C3C2H2	76	76	77	85	84	84	73	78	74

^a The acronym (RC)_{abs} is meant to denote reactant complex, (TS)_{abs} acronym is meant to denote transition state and the acronym (PC)_{abs} is meant to denote product complex.

^b The subscript “elim” in TS and PC represents the water elimination performed without inclusion of a base while the subscript “oxi” in TS and PC represents the oxidation mechanism performed without inclusion of the O₂ molecule.

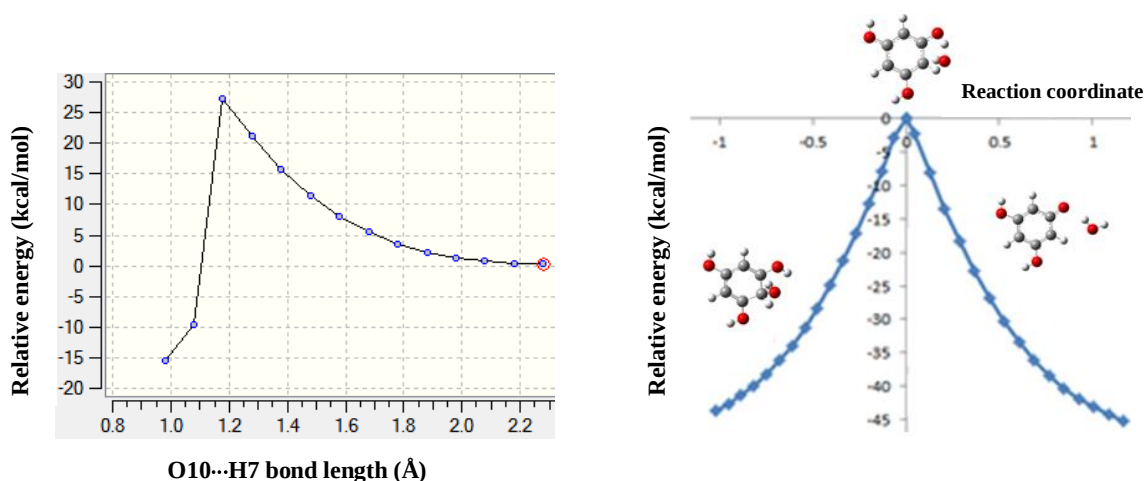


Figure 4.8: The BHLYP/6-31+G(d,p) O10···H7 bond scan (in steps of 0.1 Å) results (plot on the left) and the intrinsic reaction coordinate scan (plot on the right) for the dehydration step in the A-E mechanism.

true minima on the potential energy surface. The first minimum point and the second minimum point correspond to the intermediate species and the product complex, respectively. The structure at the maximum point is located at the O10···H7 bond distance of 1.154 Å. Optimisation followed by frequency calculations upon the structure at the maximum point on the PES gave one imaginary frequency, indicating that it is a transition state on PES. The magnitude of the imaginary frequency (cm^{-1}) is 976 *in vacuum*

medium, 814 in benzene solvent medium and 525 in ethanol solvent medium. The IRC analysis (also included in Figure 4.8) indicates that the found transition state joins the intermediate species and the product complex.

The molecular graphs for (TS)_{elim} and (PC)_{elim} are shown in Figure 4.6; (TS)_{elim} is characterised by the existence of the C3–O10 bond and the O10...H7 bond. The two bonds form part of the five member ring, which is identifiable by the existence of RCP. (PC)_{elim} represent the interaction between phenoxyl radical and a water molecule. It is characterised by the absence of the C3–O10 bond and the presence of the O10–H7 bond. The molecular graph for (PC)_{elim} shows the existence of the O10...H3 and O7...H7 intermolecular bonds and the O10–H7 intramolecular bond, giving rise to a six member ring, which is confirmed by the existence of RCP.

The electronic properties at BCPs for (TS)_{elim} and (PC)_{elim} are reported in Table 4.8. The ρ value for the C3–O10 bond is lower in (TS)_{elim} than in (IM)_{add}, implying that the electron density is less accumulated in (TS)_{elim} than in (IM)_{add}. The $\nabla^2\rho$ and H values for the C3–O10 bond and the O10...H7 bond are negative, indicating that both bonds can be described as covalent in nature. The ρ value for the O10–H7 bond in (PC)_{elim} is higher than the O10...H7 bond in (TS)_{elim}, indicating that the electron density is highly accumulated within the O10–H7 bond rather than within the O10...H7 bond. The $\nabla^2\rho$ and H values for the O10–H7 bond in (PC)_{elim} are all negative, implying that it is covalent in nature.

The relative energies for the dehydration step reaction species are reported in Table 4.9. The ΔE_{act} value (calculated as the difference between the energy of (TS)_{elim} and the energy of (IM)_{add}) is approximately 18 kcal/mol in all media. A comparison of the ΔE_{act} values for the •OH addition step and the dehydration step suggests that they are significantly higher for the dehydration step than for the •OH addition step. This implies that the dehydration step is likely to occur slower than the •OH addition. In this way, the dehydration step is considered as the rate-limiting step for the A-E mechanism.

Analysis of the complete A-E mechanism (taking into account the $\bullet\text{OH}$ addition step and the dehydration step) suggests that the enthalpy of $(\text{PC})_{\text{elim}}$ is significantly higher than the enthalpy of $(\text{RC})_{\text{add}}$, indicating that the dehydration step is exothermic and thermodynamically favoured; the energy profile for the overall mechanism is shown in Figure 4.9. A comparison of the reaction energy gap (i.e., the electronic energy difference between the product complex and the reactant complex) across the media suggests no significant variation. The Gibbs free energy is significantly lower for $(\text{PC})_{\text{elim}}$ than for $(\text{RC})_{\text{add}}$, implying that the A-E mechanism is spontaneous, albeit it is too slow, which can be identified by the high barrier height of the rate-limiting step.

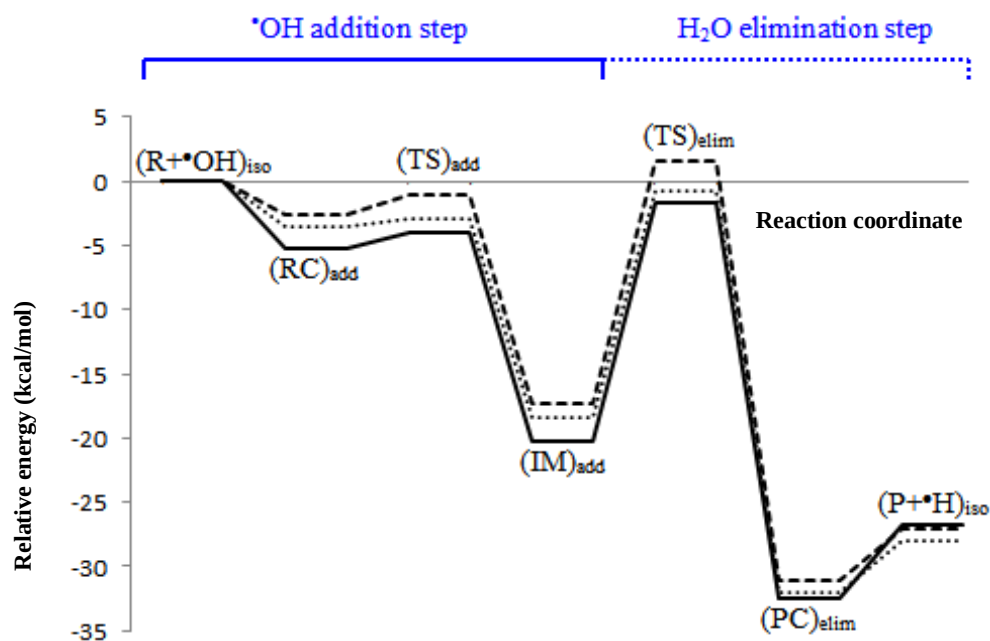


Figure 4.9: M06–2X/6-311++G(3df,2p) energy profile (potential energy versus reaction coordinate) for the reaction of $\text{FG} + \bullet\text{OH}$ through the A-E mechanism performed without addition of a catalyst; results *in vacuo* (—), in benzene (.....) and in ethanol (-----) media.

The calculated rate constant for the dehydration step performed without inclusion of a base is denoted as k_{elim} ; it is reported in Table 4.6. The k_{elim} (s^{-1}) value is 0.142 *in vacuum* medium, 0.594 in benzene solvent medium and 0.105 in ethanol solvent medium,

indicating that the reaction is significantly slow with respect to the first step of the mechanism. The findings obtained are consistent with the analysis of the ΔE_{act} values as well as the experimental findings that suggest that when the reaction is performed without inclusion of the catalyst, the A-E mechanism is too slow to yield the desired results.

4.3.3.2 Dehydration step performed with inclusion of the base

The elimination of a water molecule from $(\text{IM})_{\text{add}}$ in the presence of a hydroxyl anion (OH^-) catalyst requires two steps; the first step is the interaction of $(\text{IM})_{\text{add}}$ with OH^- catalyst, resulting in the abstraction of the proton by OH^- from $(\text{IM})_{\text{add}}$ to form trihydroxycyclohexadienone anion radical and a water molecule. The second step is the removal of OH^- anion from the trihydroxycyclohexadienone anion radical, resulting in the formation of the phenoxyl radical. The reaction species involved in the reaction are identified with a subscript “elim,base”.

The first step of the catalysed reaction involves the interaction of the OH^- with H7 in the $(\text{IM})_{\text{add}}$, performed with the aim of obtaining the reactant complex. When this reaction was performed, it resulted in a rapid abstraction of the H7 proton by the hydroxyl anion. The product species are trihydroxycyclohexadienone anion radical anion and a water molecule. The reverse MEP scan of the $\text{O7}\cdots\text{H7}$ bond, starting from trihydroxycyclohexadienone anion radical to form $(\text{IM})_{\text{add}}$, is shown in Figure 4.10; the outcome of the scan shows no barrier height, indicating that the reaction is very fast. This result is consistent with the experimental findings that base catalysed reactions are very fast [57].

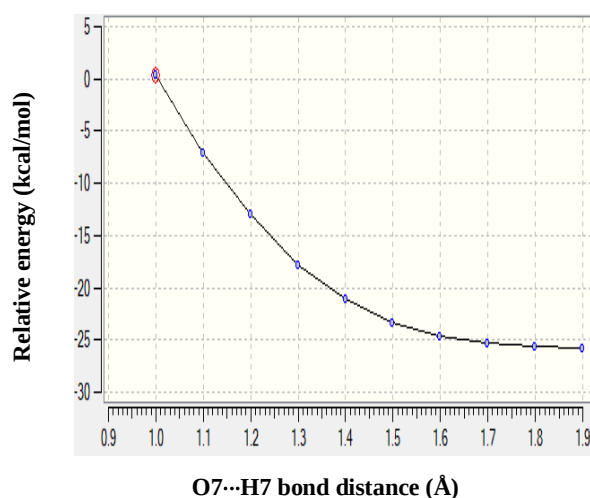


Figure 4.10: The O7...H7 bond scan (in steps of 0.1Å) starting from trihydroxycyclohexadienone anion radical for the abstraction of the H7 proton; results obtained utilising BHHLYP/6-31+G(d, p) method in ethanol. The scan is performed in steps of 0.1Å.

The removal of the OH⁻ catalyst was achieved through the scan of the C3–O10 bond; it is shown in Figure 4.11. The outcome of the scan shows three stationary points; two minima and one maximum. The first minimum is located at the C3–O10 bond distance of 1.448 Å while the second minimum is located at the C3...O10 bond distance of 2.148 Å. Optimisation followed by frequency calculations on the individual structures at each minimum gave zero imaginary frequency, indicating that they are the true minima on the potential energy surface. The structure at the first minimum is trihydroxycyclohexadienone anion radical while the structure at the second minimum is the phenoxyl radical species. The structure at the maximum is located at the C3–O10 bond distance of 1.948 Å. Optimisation and frequency calculations upon the structure at the maximum point gave one imaginary frequency of magnitude 310 cm⁻¹ in benzene and 336 cm⁻¹ in ethanol, indicating that it is a transition state on the potential energy surface.

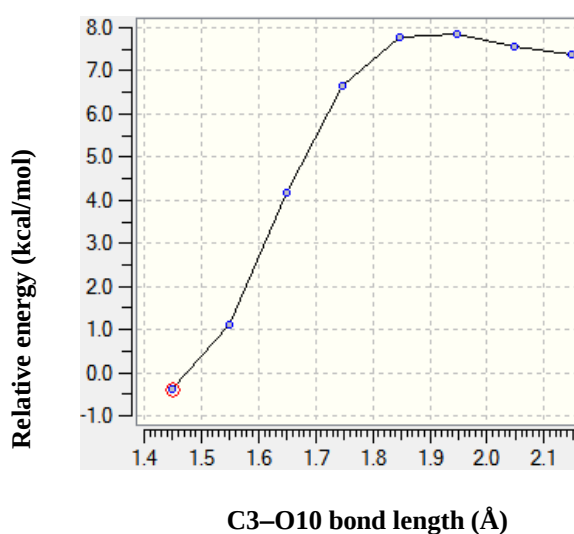


Figure 4.11: The C3–O10 bond scan (in steps of 0.1 Å) for elimination of the OH anion in trihydroxycyclohexadienone anion radical, results obtained utilising BHHLYP/6-31+G(d, p) method in ethanol.

The optimised reaction species involved in the OH[−] elimination step are shown in Figure 4.12, while the corresponding geometric properties are reported in Table 4.12. The electronic properties at BCPs and energies for the reaction species are reported in Table 4.13 and Table 4.14, respectively. The molecular graphs are shown in Figure 4.13.

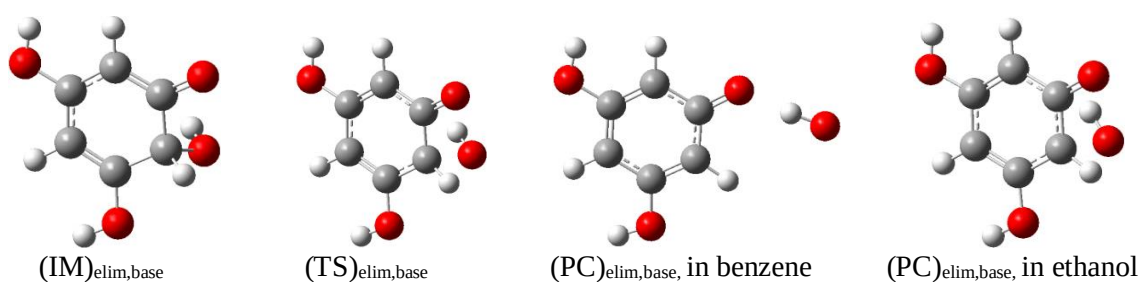


Figure 4.12: BHHLYP/6-311++G(3df, 2p) optimised reaction species for the OH[−] elimination step in A-E mechanism. Results in benzene solvent medium and ethanol solvent medium.

Table 4.12: Representative bond lengths (Å), bond angles (°) and torsion angles (°) for the OH⁻ elimination step for the A-E mechanism performed with the inclusion of the base. Results obtained utilising DFT/BHLYP calculation method.

structure ^a and parameters	BHLYP/6-31++G(d,p) results		BHLYP/6-311++G(3df, 2p) results	
	in benzene	in ethanol	in benzene	in ethanol
(IM)_{elim,base}				
C2–O7	1.256	1.285	1.247	1.274
C3–O10	1.457	1.456	1.452	1.450
O7...H10	3.212	3.214	3.19	3.200
C4–C3–O10–H10	73	65	72	64
(TS)_{elim,base}				
C2–O7	1.256	1.272	1.242	1.262
C3...O10	1.934	1.902	1.935	1.888
O7...H10	2.601	3.394	3.162	3.378
C4–C3–O10–H10	158	66	90	65
(PC)_{elim,base}				
C2–O7	1.280	1.270	1.265	1.255
C3...O10	— ^b	2.170	— ^b	2.180
O7...H10	1.544	1.569	3.297	3.300
O7–H7–O10	177	51	176	84
C2–O7–H10–O10	–176	–96	172	–99
C4–C3–O10–H10	— ^b	82	— ^b	79

^a The abbreviation IM denotes intermediate, TS denotes transition state and PC denotes product complex species

^b The C3 atom and the O10 are not interacting in the product complex obtained in benzene

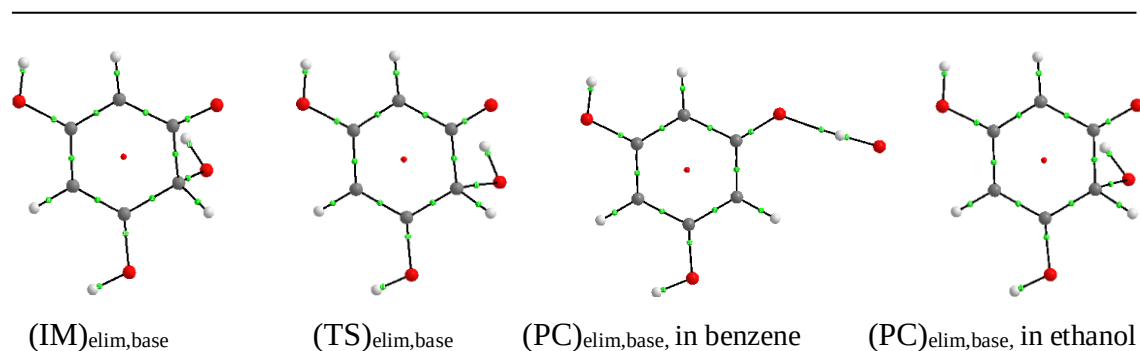


Figure 4.13: Molecular graphs for the reaction species for the OH⁻ elimination step in the A-E mechanism performed with the inclusion of the base. BHLYP/6-311++G(3df, 2p) results *in vacuo*. The small green and red dots represent the bond critical points and ring critical points, respectively.

Table 4.13: Bond critical point properties for selected bonds within the OH[−] elimination step reaction species obtained through the A-E mechanism that was performed with the inclusion of a catalyst. Results obtained utilising the BHHLYP/6-311++G(3df, 2p) calculation method.

structure ^a and bond type	electron density ρ ($e\text{\AA}^3$)	Laplacian of the electron density $\nabla\rho^2$ ($e\text{\AA}^5$)	potential electron energy density V (Hartree)	kinetic electron energy density G (Hartree)	total electron energy density H (Hartree)
BHHLYP/6-311++G(3df, 2p) results in benzene solvent medium					
(IM) _{elim,base}					
C2–O7	0.395259	−0.578834	−1.273660	0.564476	−0.70918
C3···O10	0.241451	−0.514827	−0.503956	0.187625	−0.31633
(TS) _{elim,base}					
C2–O7	0.400768	−0.592292	−1.300023	0.575975	−0.72405
C3···O10	0.083898	0.134789	−0.070628	0.052162	−0.01847
(PC) _{elim,base}					
C2–O7	0.376372	0.477990	−1.135668	0.477990	−0.65768
O7···H10	0.061347	0.049306	−0.061404	0.049306	−0.01210
BHHLYP/6-311++G(3df, 2p) results in ethanol solvent medium					
(IM) _{elim,base}					
C2–O7	0.370363	−0.643699	−1.124028	0.481552	−0.64248
C3···O10	0.241724	−0.504932	−0.512722	0.193245	−0.31948
(TS) _{elim,base}					
C2–O7	0.381389	−0.639844	−1.184013	0.512026	0.993578
C3···O10	0.091965	0.129181	−0.081735	0.057015	0.25026
(PC) _{elim,base}					
C2–O7	0.387899	−0.627010	−1.222603	0.532925	−0.68968
C3···O10	0.050699	0.115404	−0.036857	0.032854	−0.00400

^a The acronym TS denotes transition state, IM denotes intermediate species and PC denotes product complex species.

Table 4.14: Relative energy (ΔE), relative enthalpy (ΔH) and relative Gibbs free energy (ΔG) for the geometries involved in the reaction between FG with $\bullet\text{OH}$, results obtained utilising the 6-31++G(d,p) and 6-311++G(3df,2p) basis sets for the dehydration step performed with the inclusion of the base.

structure ^a	results obtained with the 6-31++G(d,p) basis set			results obtained with the 6-311++G(3df,2p) basis set		
	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative Gibbs free energy (ΔG , kcal/mol)	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative Gibbs free energy (ΔG , kcal/mol)
DFT/BHLYP results in benzene solvent medium						
(IM) _{elim, base}	0.000	0.000	0.000	0.000	0.000	0.000
(TS) _{elim, base}	8.566	8.350	8.746	9.007	8.845	9.319
(PC) _{elim, base}	-2.734	-2.747	-3.277	-1.853	-1.852	-2.632
DFT/BHLYP results obtained in ethanol solvent medium						
(IM) _{elim, base}	0.000	0.000	0.000	0.000	0.000	0.000
(TS) _{elim, base}	7.122	7.107	7.103	7.213	7.204	7.170
(PC) _{elim, base}	6.647	7.028	6.162	6.370	6.915	5.419

^a The acronym TS denotes transition state, IM denotes intermediate species and PC denotes product complex species. Subscript "elim base" represents reaction species obtained through the dehydration step in the A-E mechanism performed in the presence of a base catalyst.

The transition state ((TS)_{elim,base}) is characterised by the lengthening of the C3–O10 bond (0.52 Å in benzene and 0.47 Å in ethanol) as compared to its value in (IM)_{elim,base}. The C3–O10 bond distance is 1.935 Å in benzene and 1.888 Å in ethanol, indicating that it is more elongated in non-polar medium than in polar medium. The ρ value for the C3–O10 bond has lower value for (IM)_{elim,base} than for (TS)_{elim,base}, implying that less electrons are accumulated within the C3–O10 bond in (TS)_{elim,base}. The $\nabla^2\rho$ and H values are all positive for the C3–O10 bond in (TS)_{elim,base} for the results obtained in ethanol, indicating that the C3–O10 bond has weak interaction characters in nature. However, $\nabla^2\rho$ value is positive and H is negative for the C3–O10 bond in benzene, implying that the C3–O10 bond has a mixture of weak and strong interaction characters in nature. It is therefore meaningful to deduce that the C3–O10 bond in (TS)_{elim,base} is an intermolecular type of a bond rather than an intramolecular covalent bond.

The structure of (PC)_{elim,base} is different in non-polar medium and in polar medium; in benzene, it is characterised by the absence of the C3–O10 bond and the presence of the O7...H7 intermolecular hydrogen bond between phenoxyl radical and the OH[−] anion (characterised by the O7–H7–O10 angle of 174°); in ethanol solvent medium, (PC)_{elim,base} has the C3...O10 bond which is longer than in (TS)_{elim,base}. The explanation for the geometry difference between (PC)_{elim,base} in benzene and in ethanol could be that the eliminated OH[−] has minimal interactions with the non-polar benzene molecule while it may form strong interactions with the surrounding polar protic ethanol solvent molecules. Such interactions within the ethanol solvent would hamper the migration of OH[−] towards the phenoxyl O atom [274].

The molecular graph for (PC)_{elim,base} in benzene confirms the presence of the O7...H10 intermolecular bond in benzene and the presence of C3...O10 intermolecular bond in ethanol. The findings reported here are consistent with the analysis of the geometric parameters. The ρ value for the C3...O10 bond is lower in (PC)_{elim,base} than in (TS)_{elim,base}, implying that the electron density is accumulated more within the C3...O10 bond in (PC)_{elim,base} than in (TS)_{elim,base}. The $\nabla^2\rho$ and H values are all positive for the C3...O10

bond in ethanol and the O7...H10 bond in benzene, implying that they can be described as weak bonds in nature.

The overall energy profile for the mechanism that proceeds through $\bullet\text{OH}$ addition and subsequent water elimination, with the inclusion of the catalyst to aid the dehydration step, is shown in Figure 4.14. The ΔE_{act} value for the OH^- elimination step is 1.794 kcal/mol lower in ethanol than in benzene, implying that the OH^- elimination reaction is likely to occur quicker in the presence of a medium with high dielectric constant than in a medium with low dielectric constant. Analysis of the overall energy profile for the A-E mechanism suggests that the OH^- elimination step is slower than the dehydration step, which is a barrier-less process. A comparison of the ΔE_{act} values for the $\bullet\text{OH}$ addition step and for the OH^- elimination step suggests that the $\bullet\text{OH}$ addition step has lower ΔE_{act} values than OH^- elimination step. This implies that the OH^- elimination step is the slowest step in the A-E mechanism. Therefore, the OH^- elimination step is the rate-limiting step for the A-E mechanism performed with the inclusion of the OH^- catalyst.

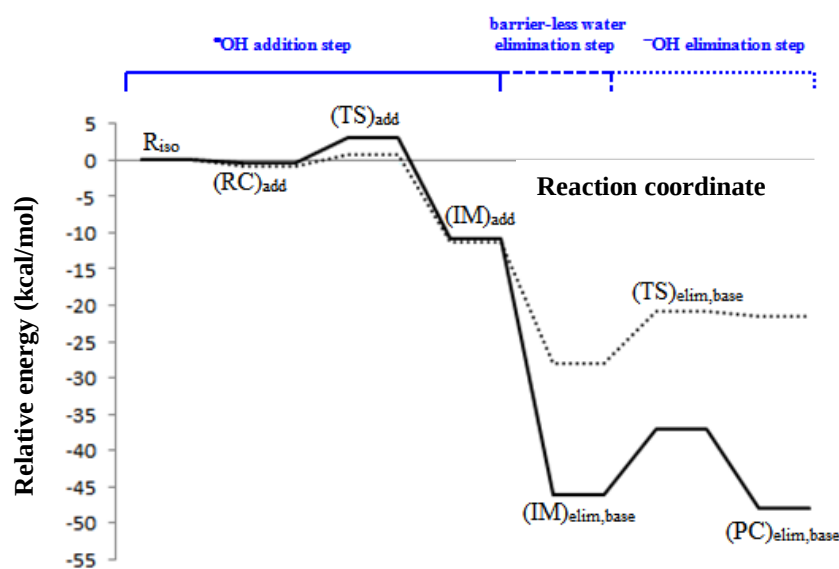


Figure 4.14: BHHLYP/6-311++G(3df, 2p) energy profile (potential energy versus reaction coordinate) for the reaction of $\text{FG} + \bullet\text{OH}$ through the A-E mechanism performed with inclusion of the base catalyst; results in benzene solvent medium (—) and in ethanol solvent medium (.....).

The enthalpy of $(PC)_{elim,base}$ is lower than the enthalpy of $(RC)_{add}$ in benzene and in ethanol, implying that the $FG + \bullet OH$ reaction through A-E mechanism in the presence of the OH^- catalyst is exothermic in nature. The results also suggest that the reaction is more thermodynamically favoured in non-polar medium than in polar medium.

The slow reaction rate associated with the reaction in the absence of a catalyst has lead experimentalists to conclude that the reaction cannot take place except with the addition of the catalyst [50]. Therefore, although theoretically, the reaction in the absence of the base appears to be thermodynamically favoured, in practice, the slow reaction rate for the mechanism limits its occurrence and it is generally accepted that water elimination step from dihydroxycyclohexadienone anion radical, for reactions involving phenol [65, 66] and trihydroxycyclohexadienone anion radical, for reactions involving phloroglucinol [50, 57], requires an addition of a catalyst, such as a base medium. The rate constant for the dehydration step for the reaction performed with inclusion of the catalyst is reported in Table 4.6; it is denoted as $k_{elim, base}$. The $k_{elim, base}$ value is higher in ethanol solvent medium than it is in benzene solvent medium, indicating that the reaction is kinetically favoured in polar medium than in non-polar medium. A comparison of the $k_{elim, base}$ for the $\bullet OH$ addition step and the OH^- elimination step indicates that the $\bullet OH$ addition step is likely to occur faster than the OH^- elimination step. Furthermore, the $k_{elim,base}$ is significantly higher than k_{elim} , implying that the reaction is kinetically favoured when the reaction is performed with inclusion of the base catalyst rather than when it is performed without the inclusion of the base catalyst. These results are in agreement with the ΔE_{act} values obtained for the reaction. In this way, it is reasonable to infer that $FG + \bullet OH$ prefers to occur through the A-E mechanism when it is performed with inclusion of the base.

4.3.4 Oxidation mechanism performed with and without the inclusion of the O_2 molecule

The reactivity of the tetrahydroxycyclohexadienyl radical, obtained in section 4.2.2, may largely depend on the reaction environment. For instance, in the presence of an O_2 molecule, the tetrahydroxycyclohexadienyl radical may proceed to produce a high order polyphenol derivative [50]. In this section, the results of the investigation on the reaction

of tetrahydroxycyclohexadienyl radical in the presence and absence of O₂ is presented in order to illustrate the possibility for the formation of high order polyphenol derivative.

4.3.4.1 Oxidation without inclusion of the O₂ molecule

Oxidation of the intermediate species in the absence of the O₂ molecule can be considered to correspond to the removal of the H3 atom from tetrahydroxycyclohexadienyl radical to form a high order polyphenol and H radical byproduct. The MEP scan for the C3–H3 bond in (IM)_{add} is shown in Figure 4.15. The scan has a minimum at the C3–H3 bond distance of 1.094 Å, a maximum structure at the C3...H3 bond distance bond distance of 1.794 Å and another minimum at the C3–H3 bond distance of 2.394 Å. Optimisation followed by frequency calculations upon the two minima resulted in structures with zero imaginary frequencies. Subsequent optimisation followed by frequency calculations on the structure at the maximum yielded one imaginary frequency, whose magnitude (cm⁻¹) is 827 *in vacuo*, 727 in benzene and 866 in ethanol media. The structure obtained at the maximum is considered as the transition state for the removal of the H radical. The structure obtained at the second minimum point is considered as the product complex while the structure at the first minimum point on the PES is (IM)_{add}. The IRC scan is also presented in Figure 4.15 and it shows that the transition state links the intermediate species and the product complex.

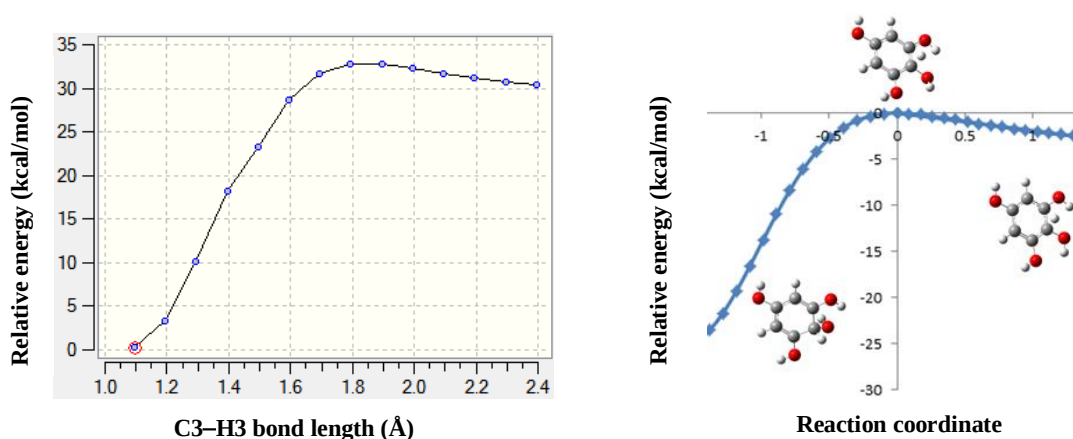


Figure 4.15: BHHLYP/6-31+G(d,p) result on the scan (in steps of 0.1 Å) for the C3–H3 bond (left) and the corresponding plot (right) for the intrinsic reaction coordinate starting from the transition state for the FG + •OH oxidation reaction without inclusion of O₂.

The optimised reaction species are shown in Figure 4.5; they are identified by the superscript “oxi”. The geometric properties for the reaction species are reported in Table 4.11. Figure 4.6 presents the reaction species’s molecular graphs while Table 4.8 reports the electronic properties at BCPs.

The transition state (symbolised as (TS)_{oxi}) is characterised by the increase in the C3–H3 bond distance in comparison to the value it has in (IM)_{add}, indicating that the C3–H3 bond is elongated in (TS)_{oxi} in comparison to the value it has in (IM)_{add}. The (TS)_{oxi} molecular graph shows the presence of the C3...H3 bond. The C3...H3 bond has lower ρ value in (TS)_{oxi} than in (IM)_{add}. The $\nabla^2\rho$ are positive while the H values are negative, suggesting that the C3...H3 bond has a mixture of weak and strong interaction characters in nature.

The product complex, denoted as (PC)_{oxi}, is characterised by the interaction between 2,3,4,6-tetrahydroxybenzene and •H. The (PC)_{oxi} molecular graph shows the existence of the C3...H3 intermolecular bond. The ρ value in the region between the C3 and H3 atoms in (PC)_{oxi} is less than its value for the C3...H3 bond in (TS)_{oxi}, indicating that the electron density is less accumulated within C3...H3 bond in (PC)_{oxi} than in (TS)_{oxi}; $\nabla^2\rho$ and H values are positive, implying that C3...H3 bond can be described as a weak bond.

The energy profile for the oxidation mechanism (including both the •OH addition and the •H elimination steps) performed in the absence of oxygen is shown in Figure 4.16. The ΔE_{act} value (kcal/mol) is 24.713 *in vacuo*, 25.309 in benzene and 26.981 in ethanol. The implication of these results is that there is a slight preference for the reaction to occur faster *in vacuo* than in polar medium. A comparison of the ΔE_{act} values obtained in the •OH addition step and that obtained in the •H elimination step suggests that the •H elimination step is likely to occur slower than the •OH addition step. The ΔE_{act} value for the rate-limiting step associated with the oxidation mechanism performed without inclusion of O₂ is higher than the ΔE_{act} value for the rate-limiting step associated with the A-E mechanism performed in the presence of a base catalyst. The change in enthalpy between the (PC)_{oxi} and (IM)_{add} indicates that the FG + •OH reaction through oxidation performed without inclusion of O₂ is endothermic in nature. $\Delta G > 0$, implying that the reaction is not spontaneous. In other words, the •H elimination step is a decomposition

reaction that requires an addition of energy into the system in order to proceed forward to produce the polyphenolic molecule.

The rate constant for the $\bullet\text{H}$ elimination step, denoted as k_{oxi} in Table 4.6, is $2.73 \times 10^{-6} \text{ s}^{-1}$ *in vacuo*, $1.08 \times 10^{-6} \text{ s}^{-1}$ in benzene and $4.67 \times 10^{-8} \text{ s}^{-1}$ in ethanol, indicating that it is a slow reaction. The k_{oxi} value is significantly lower than k_{add} value, suggesting that the $\bullet\text{H}$ elimination step is likely to occur slower than $\bullet\text{OH}$ addition step.

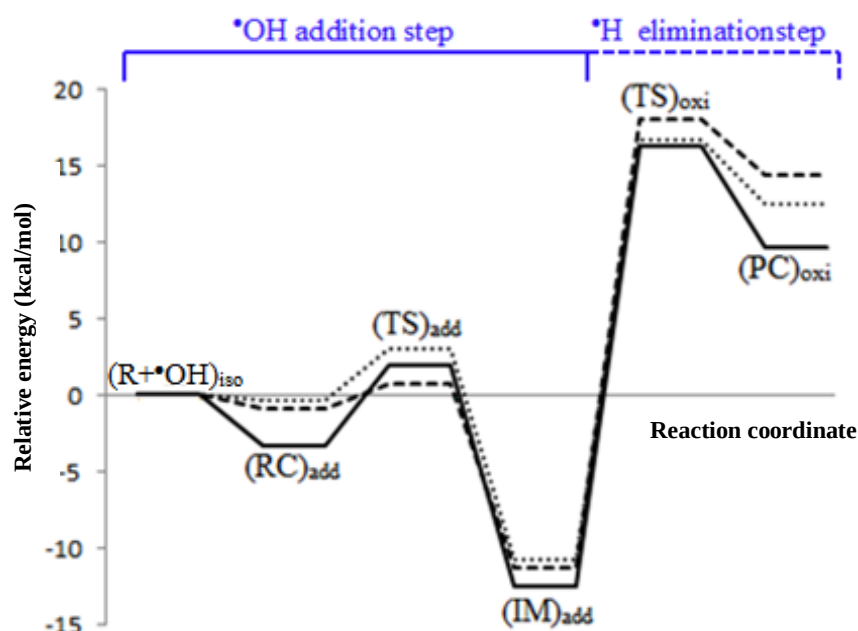


Figure 4.16: M06–2X/6-311++G(3df,2p) energy profile (potential energy versus reaction coordinate) for the reaction of $\text{FG} + \bullet\text{OH}$ through oxidation (without inclusion of O_2) of the intermediate, which was obtained after $\bullet\text{OH}$ addition to the ring; results *in vacuo* (—), in benzene (.....) and in ethanol (-----) media.

4.3.4.2 Oxidation of the intermediate with inclusion of O_2

The oxidation of $(\text{IM})_{\text{add}}$ using O_2 requires three steps; the O_2 addition step, the $\bullet\text{OOH}$ elimination step and the isomerisation step, in which trihydroxycyclohexadienone anion radical is isomerised to polyphenol. The two oxygen atoms in the isolated O_2 are labelled “11” and “12”. The reaction species obtained are identified with a subscript “oxi, O_2 ”. The

overall oxidation mechanism results in a polyphenol of high order (in comparison with the starting polyphenol) as the main product and $\bullet\text{OOH}$ as a byproduct.

The O_2 addition to $(\text{IM})_{\text{add}}$ was considered to start from a complex of $(\text{IM})_{\text{add}}$ and O_2 . The addition of O_2 can occur at either the C2 atom or the C6 atom [50, 273]; the most interesting site to consider for addition of O_2 is the C2 atom because this position is in close proximity to the C_{sp}^3 atom (section 4.2.2). The complex structure, which forms on the interaction between $(\text{IM})_{\text{add}}$ and O_2 , is hereby denoted as $(\text{IM})_{\text{oxi},\text{O}_2}$. The optimised $(\text{IM})_{\text{oxi},\text{O}_2}$ is shown in Figure 4.17; its geometric properties, molecular graph and electronic properties at the bond critical points are reported in Table 4.15, Figure 4.18 and Table 4.16, respectively. The $\text{C2}\cdots\text{O11}$ bond distance ($\text{\AA}$) in $(\text{IM})_{\text{oxi},\text{O}_2}$ has a value of 3.196 *in vacuo*, 1.510 in benzene and 3.183 in ethanol (values calculated using the M06–2X/6-311++G(3df, 2p) method. The C4-C3-O10-H10 torsion angle is approximately 64° . The molecular graph shows the existence of the $\text{C2}\cdots\text{O11}$ bond in $(\text{IM})_{\text{oxi},\text{O}_2}$. The $\nabla^2\rho$ and H values are all negative for the $\text{C2}\cdots\text{O11}$ bond, implying that it is a strong bond in nature.

The scan of the $\text{C2}\cdots\text{O11}$ bond was performed starting from $(\text{IM})_{\text{oxi},\text{O}_2}$, with the purpose of attaching the O_2 to the ring. The outcome of the scan is shown in Figure 4.19. It is characterised by the presence of a minimum point located at the $\text{C2}\cdots\text{O11}$ bond distance of 3.506 $\text{\AA}$, a maximum point located at the $\text{C2}\cdots\text{O11}$ bond distance of 2.306 $\text{\AA}$ and a minimum point located at the $\text{C2}\cdots\text{O11}$ bond distance of 1.506 $\text{\AA}$. Optimisation followed by frequency calculations on the individual structures at each minimum point resulted in zero imaginary frequencies while the structure at the maximum point gave one imaginary frequency. The structure at the first minimum is $(\text{IM})_{\text{oxi},\text{O}_2}$, the structure at the second minimum is yet another intermediate denoted as $(\text{IM}-1)_{\text{oxi},\text{O}_2}$; the structure at the maximum point is the transition state, denoted as $(\text{TS})_{\text{oxi},\text{O}_2}$. The magnitude (cm^{-1}) of the imaginary frequency for the $\text{C2}\cdots\text{O11}$ bond in $(\text{TS})_{\text{oxi},\text{O}_2}$ is 260, 255 and 279 *in vacuo*, in benzene and in ethanol, respectively.

The features of $(\text{TS})_{\text{oxi},\text{O}_2}$ and $(\text{IM}-1)_{\text{oxi},\text{O}_2}$ are also reported in Figure 4.17 for the optimised structures, Table 4.14 for the geometric properties, Figure 4.18 for the molecular graphs and Table 4.15, for the electronic properties at BCPs. $(\text{TS})_{\text{oxi},\text{O}_2}$ is

described by the shortening of the C2...O11 bond with respect to its distance in (IM)_{oxi, O2}. The C2...O11 bond is 2.815 Å *in vacuo*, 2.343 Å in benzene and 2.093 Å in ethanol, implying that the C2...O11 bond decreases with an increase in dielectric constant of the media. The molecular graph also shows the presence of the C2...O11 intermolecular bond.

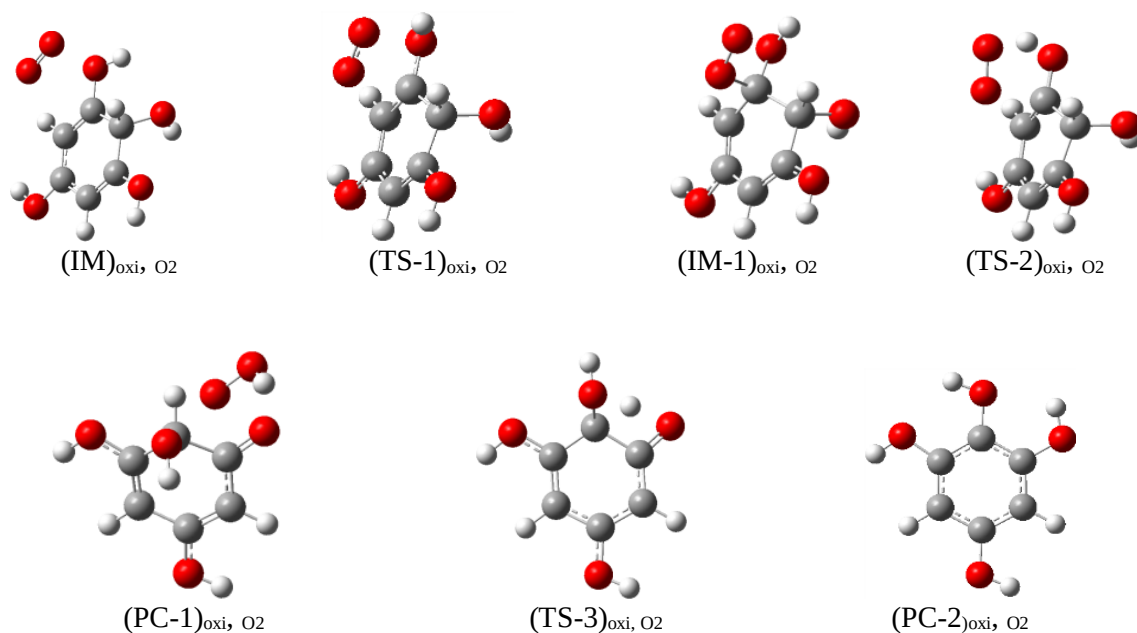


Figure 4.17: M06-2X/6-311++G(3df,2p) optimised FG + •OH reaction species through oxidation of the intermediate species, obtained after addition of •OH to the ring of FG, performed with the inclusion of O₂.

Table 4.15: Representative geometric parameters for the FG + •OH oxidation reaction species, obtained starting from the intermediate species obtained after addition of •OH to the ring of FG, performed with the inclusion of O₂.

structure ^a and parameters	DFT/M06-2X			DFT/MPW1K			DFT/BHHLYP		
	<i>in vacuo</i>	in benzene	in ethanol	<i>in vacuo</i>	in benzene	in ethanol	<i>in vacuo</i>	in benzene	in ethanol
results obtained utilising the 6-311++G(3df, 2p) basis set									
(IM) _{oxi, O2}									
C2...O11	3.197	1.510	3.184	3.860	1.494	1.506	3.585	1.495	3.558
O11...H3	2.440	2.481	2.491	3.081	2.467	2.402	2.948	2.462	1.865
C4C3O10H10	58	62	62	55	68	61	54	68	59
(TS-1) _{oxi, O2}									
C2...O11	2.815	2.343	2.093	2.781	2.248	2.094	2.054	2.272	2.135
O12...H3	2.340	2.322	2.739	2.443	2.321	2.716	2.923	2.472	2.533

O12...H7	2.338	2.547	1.469	2.148	2.518	1.537	1.333	2.294	1.910
C4C3O10H10	63	62	60	64	62	61	66	63	59
(IM-1) _{oxi, O2}									
C2...O11	1.504	1.510	1.523	1.487	1.493	1.505	1.487	1.494	1.508
O12...H3	2.406	2.414	2.427	2.390	2.399	2.403	2.395	2.403	2.419
O7...H7	0.964	0.965	0.966	0.955	0.955	0.956	0.953	0.953	0.955
O12...H7	2.298	2.349	2.456	2.276	2.324	2.445	2.344	2.394	2.480
C4C3O10H10	71	67	61	72	68	61	71	67	61
(TS-2) _{oxi, O2}									
C2...O11	2.009	2.035	2.093	2.016	2.042	2.097	2.054	2.091	2.122
O12...H7	1.270	1.301	1.457	1.279	1.317	1.522	1.333	1.394	1.870
O7...H7	1.144	1.123	1.052	1.116	1.092	1.018	1.088	1.058	0.974
C2...O7	1.365	1.363	1.365	1.356	1.354	1.356	1.360	1.358	1.360
C32C2O7H7	-91	-89	-76	-91	-89	-74	-88	-84	-53
(PC-1) _{oxi, O2}									
C2...O7	1.223	1.229	1.241	1.222	1.223	1.228	1.219	1.227	1.230
O12...H7	0.994	0.999	1.023	0.979	0.981	0.986	0.974	0.986	0.980
O7...H7	1.710	1.659	1.529	1.748	1.772	1.714	1.783	1.687	1.753
O11...H3	2.562	2.560	3.035	2.802	2.439	2.843	2.761	3.755	3.458
C32C2O7H7	-72	-69	-7	-79	9	-48	-72	-12	-87
(TS-3) _{oxi, O2}									
C2...O7	1.279	1.284	1.309	1.273	1.278	1.298	1.271	1.275	1.297
O7...H3	1.314	1.317	1.364	1.295	1.297	1.325	1.288	1.289	1.314
C3...H3	1.424	1.423	1.409	1.421	1.420	1.410	1.437	1.436	1.425
C4C3O10H10	-110	-108	-99	-115	-112	-110	-115	-113	-110
(PC-2) _{oxi, O2}									
C2...O7	1.352	1.352	1.357	1.340	1.340	1.346	1.344	1.343	1.358
O7...H3	0.963	0.964	0.966	0.954	0.955	0.956	0.953	0.953	0.966
O10...H3	2.174	2.179	2.221	2.161	2.166	2.211	2.179	2.183	2.221
C4C3O10H10	0	0	0	0	0	0	0	0	0

^a The abbreviation RC stands for reactant complex, TS stands for transition state, IM stands for intermediate and P_{iso} denotes isolated product species.

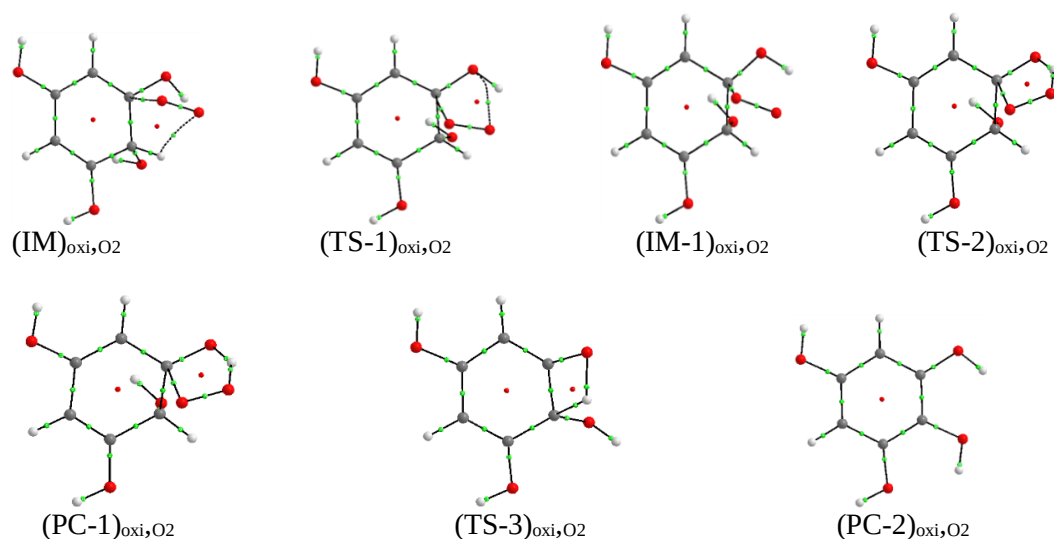


Figure 4.18: Molecular graphs for the FG + •OH reaction species involved in oxidation performed with inclusion of O₂. The green dot within a given bond represents the bond critical point while the red dot within a given ring stands for the ring critical point.

Table 4.16: M06–2X/6-311++G(3df, 2p) bond critical point properties for selected bonds within the FG + •OH oxidation reaction species obtained with inclusion of O₂

structure ^a and bond type	electron density ρ ($e\text{\AA}^3$)	Laplacian of the electron density $\nabla^2\rho^2$ ($e\text{\AA}^5$)	potential electron energy density V (Hartree)	kinetic electron energy density G (Hartree)	total electron energy density H (Hartree)
(IM) _{oxi,O2}					
C2...O11	0.013092	0.042853	−0.008393	0.009553	0.00116
O11–H3	0.566247	−0.888139	−1.271779	0.524872	−0.746907
(TS-1) _{oxi,O2}					
C2...O11	0.038777	0.095606	−0.027479	0.025690	−0.001789
(IM-1) _{oxi,O2}					
C2–O11	0.223778	−0.443991	−0.373485	0.131244	−0.242241
(TS-2) _{oxi,O2}					
C2–O7	0.073576	0.115824	−0.061075	0.045015	−0.01606
O12–H 3	0.151199	−0.137448	−0.202850	0.084244	−0.118606
O12–H7					
O7–H7	0.203565	−0.641901	−0.347856	0.093690	−0.254166
(PC-1) _{oxi,O2}					
C2–O7	0.073576	0.115824	−0.061075	0.045015	−0.01606
O12–H 3	0.151199	−0.137448	−0.202850	0.084244	−0.118606
O7–H7	0.203565	−0.641901	−0.347856	0.093690	−0.254166
(TS-3) _{oxi,O2}					
C3–H3	0.120949	−0.101732	−0.119691	0.047129	−0.072562
O7...H3	0.137772	−0.049646	−0.176419	0.082004	−0.094415
(PC-2) _{oxi,O2}					
O7–H3	0.366511	−2.784616	−0.832786	0.068316	−0.76447

^aThe abbreviation RC stands for reactant complex, TS stands for transition state, IM stands for intermediate and PC denotes product complex

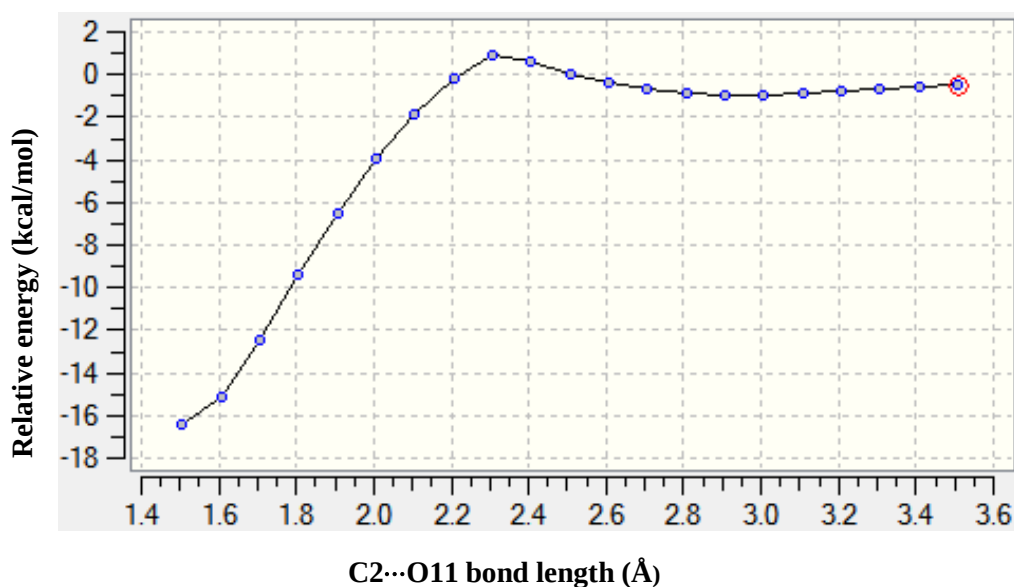


Figure 4.19: The C2...O11 bond scan (in steps of 0.1Å) for the addition of O₂ to tetrahydroxycyclohexadienyl radical, results *in vacuo* obtained utilising the M06–2X/6-31+G(d,p) calculation method.

The C2...O11 bond has higher ρ value in (TS-1)_{oxi,O2} than in (IM)_{oxi,O2}, indicating that the electron density is more accumulated in (TS-1)_{oxi,O2} than in (IM)_{oxi,O2}; it is for this reason that the C2...O11 bond is shorter in (TS-1)_{oxi,O2} than in (IM)_{oxi,O2}. The $\nabla^2\rho$ and H values are all positive for the C2...O11 bond in (TS)_{oxi,O2}, implying that the C2...O11 bond is non-covalent in nature. The intermediate species ((IM-1)_{oxi,O2}) is tetrahydroxycyclohexadienylperoxyl radical; it is described by the existence of the C2–O11 covalent bond. In this structure, the C2–O11 bond distance is 1.504 Å *in vacuo*, 1.510 Å in benzene and 1.523 Å in ethanol. The $\nabla^2\rho$ and H values are all negative for the C2–O11 bond, implying that it has strong interaction characters in nature; it can therefore be considered to be covalent in nature, albeit elongated in respect to the standard C–O bond distance, which is 1.42 Å [274].

The relative energies for the reaction species, related to the formation of tetrahydroxycyclohexadienylperoxyl radical, are reported in Table 4.17. The ΔE_{act} (kcal/mol) value is highest in benzene (13.992), intermediary in ethanol (8.124) and lowest *in vacuo* (2.399), which suggest that the addition of the O₂ molecule is most preferable *in vacuo*. The rate constant ($k_{1,O2}$) for the O₂ addition step is reported in Table 4.6; it is $1.77 \times 10^9 \text{ s}^{-1}$ *in vacuo*, $1.27 \times 10^3 \text{ s}^{-1}$ in benzene and $9.61 \times 10^6 \text{ s}^{-1}$ in ethanol, indicating that the reaction is more kinetically preferred *in vacuo* than in the presence of the solvent, which is consistent with the results obtained from the energetic parameters. A comparison of the $k_{1,O2}$ value and the k_{oxi} value (corresponding to the oxidation in the absence of O₂) suggests that the tetrahydroxycyclohexadienylperoxyl radical formation through the O₂ addition step is kinetically preferred than the formation of 2,3,4,6-tetrahydroxybenzene through oxidation without inclusion of O₂.

Table 4.17: Relative electronic energy (ΔE , kcal/mol), enthalpy (ΔH , kcal/mol) and Gibbs free energy (ΔG , kcal/mol) for the FG + $\bullet\text{OH}$ oxidation reaction species obtained when oxidation is performed with inclusion of O_2 .

structure ^a	results obtained with the 6-31++G(d,p) basis set			results obtained with the 6-311++G(3df,2p) basis set		
	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative free energy (ΔG , kcal/mol)	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative free energy (ΔG , kcal/mol)
DFT/ M06-2X results obtained <i>in vacuo</i>						
(IM) _{oxi,O2}	0.000	0.000	0.000	0.000	0.000	0.000
(TS-1) _{oxi,O2}	2.2672	1.450	3.992	2.399	1.489	4.806
(IM-1) _{oxi,O2}	-12.718	-13.978	-10.109	-11.894	-13.190	-8.703
(TS-2) _{oxi,O2}	-4.324	-5.697	-1.944	-3.786	-5.238	-0.771
(PC-1) _{oxi,O2}	-0.887	-1.187	5.961	-1.206	-1.543	-10.055
(TS-3) _{oxi,O2}	55.388	54.962	62.673	55.564	55.110	47.126
(PC-2) _{oxi,O2}	-24.223	-24.331	-16.975	-24.576	-24.824	-32.915
DFT/ M06-2X results obtained in benzene solvent medium						
(IM) _{oxi,O2}	0.000	0.000	0.000	0.000	0.000	0.000
(TS-1) _{oxi,O2}	14.654	15.144	13.577	13.992	14.381	13.186
(IM-1) _{oxi,O2}	-0.038	-0.001	-0.0722	-0.021	0.003	-0.032
(TS-2) _{oxi,O2}	7.893	7.703	7.751	7.568	7.356	7.467
(PC-1) _{oxi,O2}	7.917	8.816	-3.962	7.019	7.9167	-4.912
(TS-3) _{oxi,O2}	65.028	22.520	53.506	64.532	65.324	52.996
(PC-2) _{oxi,O2}	-12.773	-11.642	-24.377	-13.857	-12.831	-25.323
DFT/ M06-2X results obtained in ethanol solvent medium						
(IM) _{oxi,O2}	0.000	0.000	0.000	0.000	0.000	0.000
(TS-1) _{oxi,O2}	8.110	7.939	7.8859	8.124	7.907	7.894
(IM-1) _{oxi,O2}	-0.055	-0.014	-0.099	0.085	0.040	0.136
(TS-2) _{oxi,O2}	7.937	7.829	7.628	7.920	7.7629	7.609
(PC-1) _{oxi,O2}	2.565	3.582	-9.497	2.166	3.019	-9.629
(TS-3) _{oxi,O2}	61.296	62.110	49.642	61.108	61.885	49.462
(PC-2) _{oxi,O2}	-13.709	-12.607	-25.307	-14.561	-13.608	-25.993
DFT/MPW1K results obtained <i>in vacuo</i>						
(IM) _{oxi,O2}	0.000	0.000	0.000	0.000	0.000	0.000
(TS-1) _{oxi,O2}	12.715	10.909	18.843	12.490	10.601	18.665
(IM-1) _{oxi,O2}	-8.258	-9.982	-1.948	-7.610	-9.306	-1.522
(TS-2) _{oxi,O2}	0.3056	-1.580	6.436	0.700	-1.177	6.643
(PC-1) _{oxi,O2}	-0.427	-1.233	-6.089	-0.601	-1.393	-6.4131
(TS-3) _{oxi,O2}	56.540	55.609	51.326	56.567	55.664	51.135
(PC-2) _{oxi,O2}	-23.621	-24.233	-28.885	-23.763	-24.41	-29.165
DFT/MPW1K results obtained in benzene solvent medium						
(IM) _{oxi,O2}	0.000	0.000	0.000	0.000	0.000	0.000
(TS-1) _{oxi,O2}	21.051	20.518	21.473	12.634	13.023	11.711
(IM-1) _{oxi,O2}	0.058	0.040	0.096	0.047	0.029	0.100
(TS-2) _{oxi,O2}	7.784	7.570	7.681	7.589	7.357	7.525
(PC-1) _{oxi,O2}	3.645	4.512	-8.163	3.000	3.855	-8.780
(TS-3) _{oxi,O2}	61.631	62.366	50.201	61.131	61.871	49.715
(PC-2) _{oxi,O2}	-16.736	-15.639	-28.264	-17.521	-16.493	-28.939
DFT/MPW1K results obtained in ethanol solvent medium						
(IM) _{oxi,O2}	0.000	0.000	0.000	0.000	0.000	0.000
(TS-1) _{oxi,O2}	7.600	7.535	7.220	7.728	7.630	7.3745
(IM-1) _{oxi,O2}	-0.178	-0.075	-0.322	-0.047	-0.019	-0.080
(TS-2) _{oxi,O2}	24.142	23.672	24.626	7.295	7.328	6.695
(PC-1) _{oxi,O2}	-2.351	-1.357	-14.377	-2.667	-1.660	-14.709
(TS-3) _{oxi,O2}	58.014	58.836	46.360	57.810	58.621	46.191
(PC-2) _{oxi,O2}	-17.517	-16.386	-29.170	-18.183	-17.114	-29.744
DFT/BHLYP results obtained <i>in vacuo</i>						
(IM) _{oxi,O2}	0.000	0.000	0.000	0.000	0.000	0.000
(TS-1) _{oxi,O2}	6.337	5.043	10.677	6.912	5.618	11.206
(IM-1) _{oxi,O2}	-6.989	-8.657	-1.822	-6.091	-7.719	-1.034
(TS-2) _{oxi,O2}	2.944	1.123	7.916	3.624	1.828	8.517
(PC-1) _{oxi,O2}	-2.547	-3.288	-9.546	-2.753	-3.480	-9.735
(TS-3) _{oxi,O2}	58.717	57.818	52.385	58.987	58.124	52.560
(PC-2) _{oxi,O2}	-24.339	-24.905	-30.739	-24.596	-25.201	-31.003

DFT/BHLYP results obtained in benzene solvent medium						
(IM) _{oxi,O2}	0.000	0.000	0.000	0.000	0.000	0.000
(TS-1) _{oxi,O2}	12.826	13.280	11.780	12.464	12.883	11.448
(IM-1) _{oxi,O2}	0.069	0.060	0.072	0.046	0.035	0.070
(TS-2) _{oxi,O2}	8.977	8.788	8.798	8.784	8.588	8.616
(PC-1) _{oxi,O2}	0.324	1.211	-11.696	-0.633	0.228	-12.523
(TS-3) _{oxi,O2}	62.663	63.392	51.202	62.060	62.789	50.630
(PC-2) _{oxi,O2}	-18.567	-17.463	-30.137	-19.740	-18.719	-31.186
DFT/BHLYP results obtained in ethanol solvent medium						
(IM) _{oxi,O2}	0.000	0.000	0.000	0.000	0.000	0.000
(TS-1) _{oxi,O2}	3.296	3.072	4.336	2.870	2.125	4.893
(IM-1) _{oxi,O2}	-14.083	-13.880	-15.119	-4.820	-5.581	-2.459
(TS-2) _{oxi,O2}	2.889	2.797	3.644	2.523	1.891	4.292
(PC-1) _{oxi,O2}	-9.627	-8.952	-20.146	-10.717	-10.568	-20.232
(TS-3) _{oxi,O2}	54.859	55.432	44.583	54.248	54.281	44.996
(PC-2) _{oxi,O2}	-23.309	-22.459	-33.543	-24.783	-24.526	-33.928

^a The abbreviation RC stands for reactant complex, TS denotes transition state, IM stands for the intermediate species, PC stands for product complex and P_{iso} denotes isolated product species, respectively

The second step after the addition of the O₂ molecule to (IM)_{add} to form (IM-1)_{oxi,O2}, is the removal of •OOH from (IM-1)_{oxi,O2} to form trihydroxycyclohexadienone anion radical. The elimination of •OOH was achieved by scanning the O12...H2 bond in order to abstract H2 and bond it to O12 (the O atom of the O₂ molecule that is not bonded to the ring). The scan is shown in Figure 4.20; it has two minima points, one minimum occurring at the O12...H2 bond distance of 1.506 Å and the other minimum point occurring at O12...H2 bond distance 2.906 Å. It also has one maximum point, which occurs at the O12...H2 bond distance of 2.106 Å. The first minimum point corresponds to (IM-1)_{oxi,O2}. The second minimum point has zero imaginary point and it corresponds to a product complex ((PC-1)_{oxi,O2}) structure after the addition of O₂. The structure found at the maximum corresponds to the transition state ((TS-2)_{oxi,O2}) structure because it has one imaginary frequency; The imaginary frequency corresponds to simultaneous vibrations of the C2...O11 bond and O12...H2 atoms and its magnitude (cm⁻¹) is 739 *in vacuo*, 593 in benzene and 292 in ethanol.

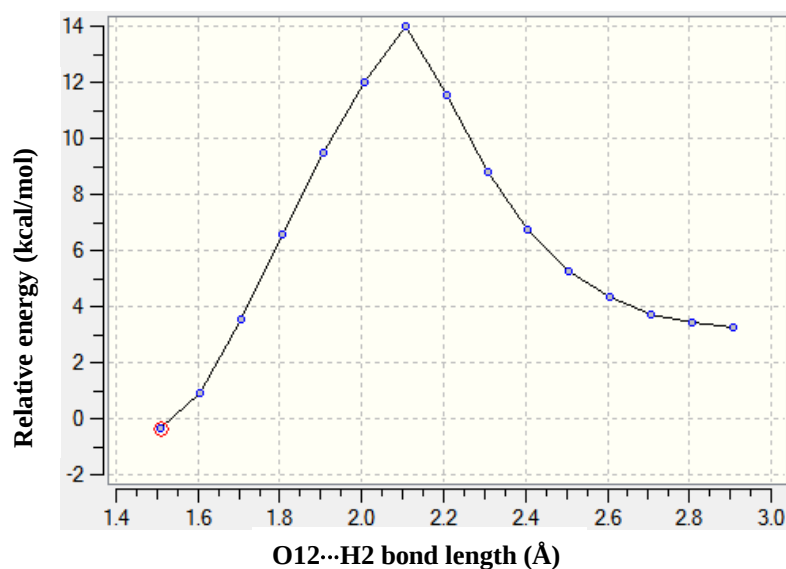


Figure 4.20: M06–2X/6-31+G(d, p) result on the scan (in steps of 0.1 Å) for the O12...H2 bond corresponding to the FG + •OH oxidation reaction performed with inclusion of O₂.

The features of (TS-2)_{oxi,O2} and (PC-1)_{oxi,O2} are included in Figure 4.17 for the optimised structures, Table 4.15 for the geometric properties, Figure 4.18 for the molecular graphs and Table 4.16, for the electronic properties at BCPs; the corresponding relative energies are reported in Table 4.17. (TS-2)_{oxi,O2} is characterised by the elongation of the O7–H7 and C2–O11 bonds as well as the shortening of the C12...H7 bond in comparison with their respective values in (IM-1)_{oxi,O2}. The molecular graph shows the presence of the C12...H7 bond, which forms part of the five member ring that is identifiable by a ring critical point. The C12...H7 bond has higher ρ value in (TS-2)_{oxi,O2} than in (IM-1)_{oxi,O2}. The O7–H7 and C2–O11 bonds have lower ρ values in (TS-2)_{oxi,O2} than in (IM-1)_{oxi,O2}, implying that the electrons are less accumulated within the O7–H7 and C2–O11 bonds in (TS-2)_{oxi,O2} than in (IM-1)_{oxi,O2}. The $\nabla^2\rho$ value is positive and the H value is negative for the C12...H7 bond, indicating that it has a mixture of weak and strong interaction characters in nature. (PC-1)_{oxi,O2} is characterised by the interaction between trihydroxycyclohexadienone anion radical and •OOH. The molecular graph shows the

presence of the O7...H7 bond and the C2...O11 bond. The $\nabla^2\rho$ and H values for the O12-H7 are all positive, implying that the O7...H7 bond and the C2...O11 bond are covalent in nature.

The ΔE_{act} (kcal/mol) corresponding to the $\bullet\text{OOH}$ elimination step is 8.108 for the results *in vacuo*, 7.589 for the results in benzene medium and 7.835 for the results obtained in ethanol medium. The ΔE_{act} value is lower for the $\bullet\text{OOH}$ elimination step than for the O_2 addition step in benzene and in ethanol; however, it is higher for the $\bullet\text{OOH}$ removal step than for the O_2 addition step *in vacuo*, implying that the $\bullet\text{OOH}$ removal step is likely to occur slower than the O_2 addition step in polar and non-polar media. In gaseous phase, the $\bullet\text{OOH}$ removal step is likely to occur faster than O_2 addition step. The rate constant for the elimination of $\bullet\text{OOH}$ from tetrahydroxycyclohexadienylperoxyl radical is denoted as k_{2,O_2} ; its magnitude (s^{-1}) is of the order of 10^5 – 10^7 , which is similar to the rate constant of $1.35 \times 10^5 \text{ s}^{-1}$ reported for the elimination of the $\bullet\text{OOH}$ from the dihydroxycyclohexadienylperoxyl radical [57, 274–276]. The k_{2,O_2} value is $9.020 \times 10^6 \text{ s}^{-1}$ *in vacuo*, $1.87 \times 10^7 \text{ s}^{-1}$ in benzene and $1.95 \times 10^7 \text{ s}^{-1}$ in ethanol media, indicating that the media minimally affect the k_{2,O_2} value. A comparison between the k_{2,O_2} value and the k_{1,O_2} suggests that k_{2,O_2} value is higher in benzene and in ethanol while it is lower *in vacuo* than k_{1,O_2} . The rate constants obtained are in agreement with the ΔE_{act} values for the reaction.

(PC-1) $_{\text{oxi},\text{O}_2}$ exist in a keto form. However, it can undergo the *keto-enol* tautomerism type of rearrangement in order to exist in equilibrium with its enol form, which is 2,3,4,6-tetrahydroxybenzene. The interconversion between the two forms may involve the transfer of H3 (which is an alpha hydrogen atom) to O7 and the reorganisation of bonding electrons. Tautomerism is recognised as another type of structural isomerism; it is often significant to establish the most stable form of the compound between the keto (i.e., trihydroxycyclohexadienone anion radical) and the enol (i.e., 2,3,4,6-tetrahydroxybenzene).

The isomerisation of (PC-1)_{oxi,O2}, is achieved through the scan of O7...H3 bond starting from (PC-1)_{oxi,O2} to form 2,3,4,6-tetrahydroxybenzene (which is denoted as (PC-2)_{oxi,O2}). The scan is shown in Figure 4.21; it has a minimum point at the O7...H2 bond distance of

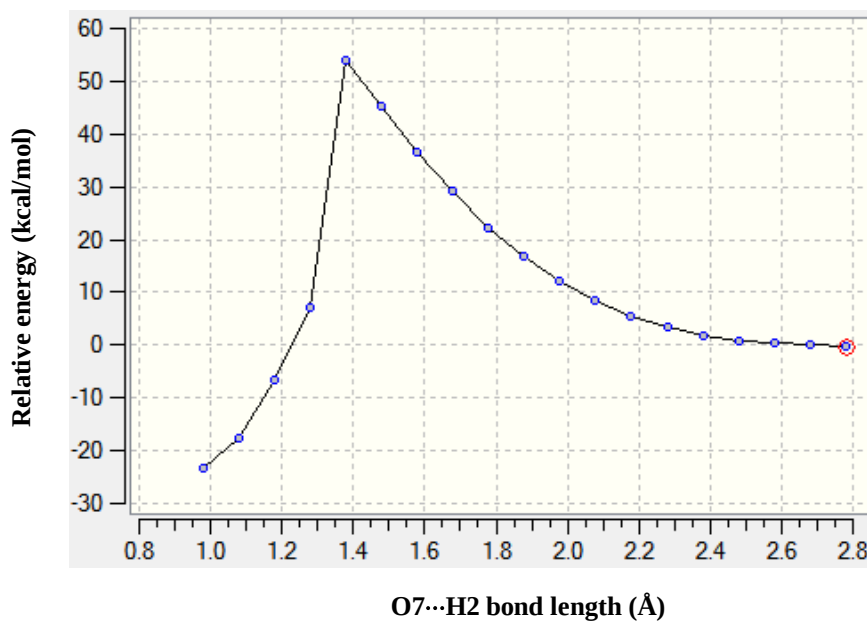


Figure 4.21: M06–2X/6-31+G(d, p) results corresponding to the O7...H3 bond scan (in steps of 0.1 Å) leading to the isomerisation of trihydroxycyclohexadienone anion radical.

2.779 Å, which corresponds to (PC-1)_{oxi,O2} and a minimum point at the O7...H2 bond distance of 0.979 Å, which corresponds to (PC-2)_{oxi,O2}. Optimisation followed by the frequency calculations upon the individual structures at each minimum point gave zero imaginary frequency. The scan also has a maximum point which is located at the O7...H2 bond distance of 1.379 Å; after geometry optimisation and frequency calculations, it was found that it has one imaginary frequency of magnitude (cm⁻¹) 2169 for the results obtained *in vacuo*, 2178 for the results obtained in benzene medium and 2195 for the results obtained in ethanol medium. This structure can therefore be considered as the transition state connecting (PC-1)_{oxi,O2} and (PC-2)_{oxi,O2}; it is labelled as (TS-3)_{oxi,O2};

The features of (TS-3)_{oxi,O2} and (PC-2)_{oxi,O2} are included in Figure 4.17 for the optimised structures, Table 4.15 for the geometric properties, Figure 4.18 for the molecular graphs and Table 4.16, for the electronic properties at BCPs; the relative energies are reported in Table 4.17 along with the energies of all the structures comprising the oxidation mechanism in the presence of O₂. (TS-3)_{oxi,O2} is characterised by the elongation of the C2–H3 and the shortening of the O7...H3 bonds in comparison with their respective distances in (PC-1)_{oxi,O2}. The molecular graph shows the existence of the C2–H3 and O7...H3 bonds, which form part of the four member ring; it is identified by the existence of RCP. The ρ value for the C2–H3 bond decreases while the ρ value for the O7...H3 bond increases in (TS-3)_{oxi,O2} in comparison with the value it has in (PC-1)_{oxi,O2}. The $\nabla\rho^2$ value and the H value are all positive for the C2–H3 and O7...H3 bonds, indicating that the C2–H3 and O7...H3 bonds have strong interaction characters in nature.

A comparison of the energies of (PC-1)_{oxi,O2} and (PC-2)_{oxi,O2} suggests that (PC-2)_{oxi,O2} has significantly lower energy than (PC-1)_{oxi,O2}, which implies that (PC-2)_{oxi,O2} is more stable than (PC-1)_{oxi,O2}. In other words, the rearrangement reaction for the formation of 2, 3, 4, 6-tetrahydroxybenzene from trihydroxycyclohexadienone anion radical is a favourable process. However, an analysis of ΔE_{act} value for the isomerisation step (which is approximately 70 kcal/mol in all the media), suggests that although the reaction is favourable, it is a slow process since the barrier height is significantly high.

The overall energy profile for the oxidation mechanism in the presence of O₂ is shown in Figure 4.22. The ΔE_{act} value for the isomerisation step has a higher barrier height than the O₂ addition step and the •OOH elimination step. In this way, the isomerisation step is considered as the rate-limiting step for the overall mechanism.

The enthalpy value is significantly lower for (PC-2)_{oxi,O2} than for the (RC)_{add}, suggesting that the overall oxidation reaction is an energy releasing reaction. A comparison of the change in enthalpy between the oxidation mechanism performed with and without inclusion of the O₂ molecule suggests that oxidation reaction is exothermic when it is performed with inclusion of O₂ and endothermic when it is performed without inclusion of O₂. The Gibbs free energy value is significantly lower for (PC-2)_{oxi,O2} than for (RC)_{add},

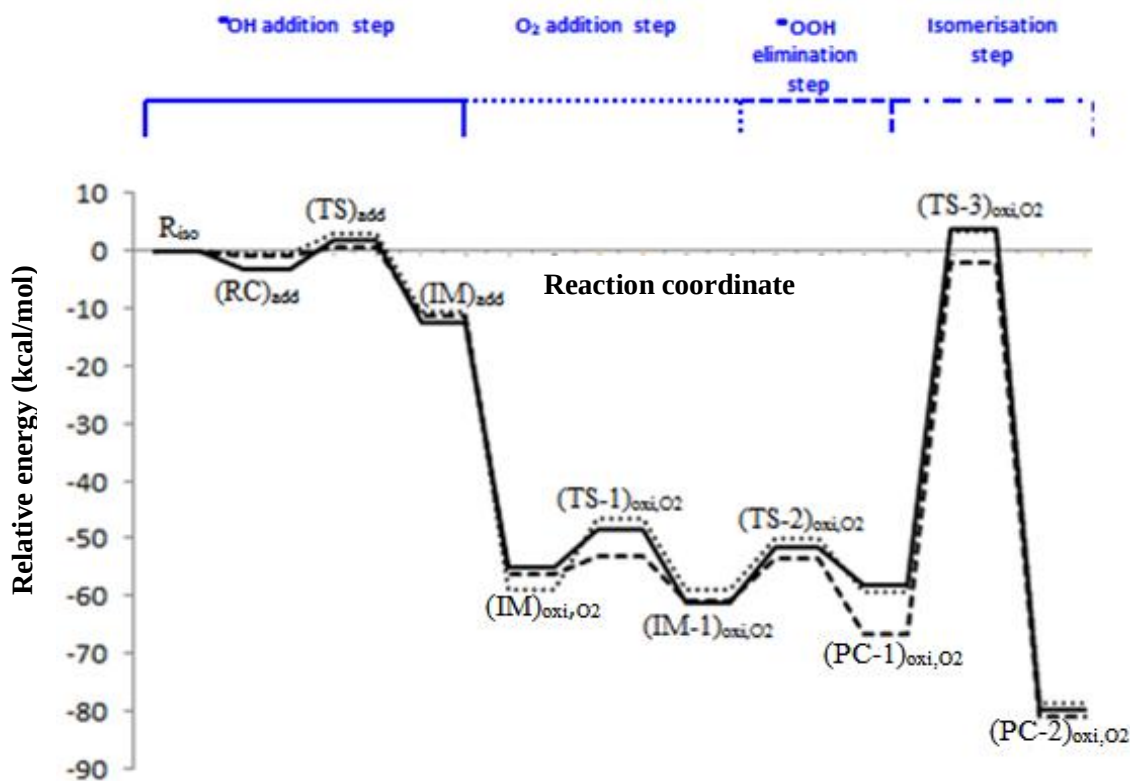


Figure 4.22: BHHLYP/6-311++G(3df, 2p) Energy profile (potential energy versus reaction coordinate) for the FG + •OH oxidation reaction with inclusion of the O₂ molecule. Results *in vacuo* (—) in benzene (.....) and in ethanol (-----) media.

indicating that the FG + •OH reaction through the oxidation mechanism performed with inclusion of the O₂ molecule is spontaneous.

The rate constant for the isomerisation step is denoted as k_{3,O_2} ; it is $7.14 \times 10^{-30} \text{ s}^{-1}$ *in vacuo*, $2.09 \times 10^{-30} \text{ s}^{-1}$ in benzene and $2.85 \times 10^{-31} \text{ s}^{-1}$ in ethanol media, implying that it is a very slow step. There is minimal difference among the k_{3,O_2} values obtained in different media. A comparison of k_{3,O_2} , k_{2,O_2} and k_{1,O_2} values suggests that the isomerisation step is significantly slower than the O₂ addition step and the •OOH elimination step. In this way, the k_{3,O_2} values are consistent with the barrier heights obtained for isomerisation step.

In summary, the FG + $\bullet$ OH reaction prefers occurring through the HAT mechanism to occurring through the SET and SPLET mechanism to yield the phenoxyl radical. The phenoxyl radical prefers forming through the A-E mechanism, which involves the $\bullet$ OH addition step followed by the dehydration step, to the DHAA mechanism. In other words, FG + $\bullet$ OH yields the phenoxyl radical through the A-E mechanism under basic conditions, which is consistent with the experimental studies for FG + $\bullet$ OH [50]. However, under neutral conditions and in the presence of O₂ molecule, FG + $\bullet$ OH undergoes oxidation to yield 2,3,4,6-tetrahydroxybenzene. The implication of the findings reported here is that investigations on the reactions of phloroglucinol derivatives with $\bullet$ OH should largely be considered to proceed through the addition mechanism.

4.4 THAP + $\bullet$ OH reaction

This section reports and discusses results on the reaction mechanism involved in the THAP + $\bullet$ OH reaction; it considers only the reaction mechanism occurring at the *ortho* reaction site, since the reaction mechanism occurring at the *para* reaction site has been considered to have less contribution to the $\bullet$ OH scavenging ability of acylated phloroglucinol derivatives (section 4.2). The results obtained are presented in such a way that the trends across geometric, energetic, electronic and kinetic parameters are analysed and compared to establish similarities in trends among different parameters. Since acylated phloroglucinol derivatives are essentially a special type of phloroglucinol derivatives, it was determined that investigation THAP + $\bullet$ OH is proceeded through only the addition mechanisms; in other words, the DHAA mechanism has been omitted because of the fact that it is not the most preferred mechanism for FG + $\bullet$ OH.

4.4.1 $\bullet$ OH addition step towards addition-elimination and oxidation

THAP + $\bullet$ OH was initiated by considering that the addition of $\bullet$ OH on THAP would take place at C3, which is located at a *meta* position with respect to the *acyl* group (Figure 1.1). The interaction of the THAP molecule and $\bullet$ OH results in the formation of the

reactant complex; it is denoted as $(RC^{\tau})_{add}$. Figure 4.23 shows the optimised structure, together with the representative bond lengths of $(RC^{\tau})_{add}$; it is characterised by the presence of three non-covalent bonds; O12...H9 intramolecular hydrogen bond, O13...H7 intermolecular hydrogen bonds and C3...O13 intermolecular interaction.

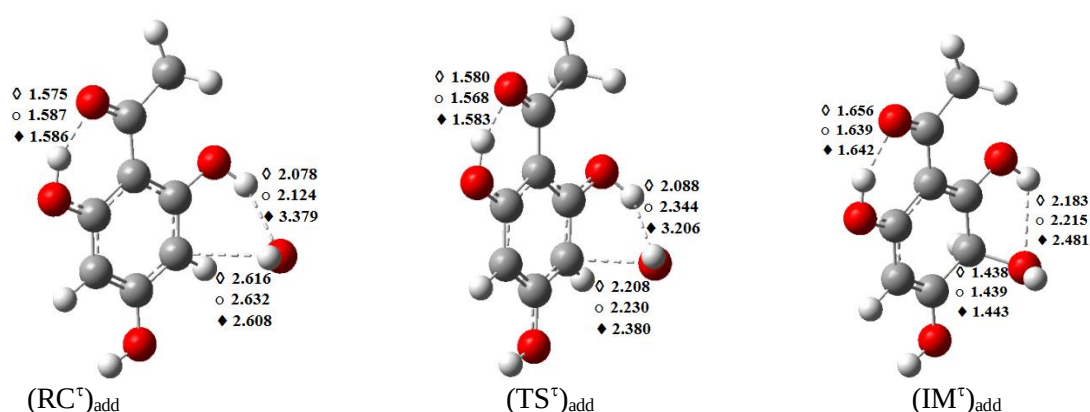


Figure 4.23: M06–2X/6-311++G(3df,2p) reaction species involved in the $\bullet OH$ addition step for the THAP + $\bullet OH$ reaction; the subscript “add” denotes species obtained from $\bullet OH$ addition step. The selected bond lengths for the non-covalent interactions in the different reaction species are obtained in vacuum ($\diamond$), in benzene solvent medium ($\circ$) and in ethanol solvent ($\blacklozenge$) medium. The acronym RC^{τ} denotes reactant complex, TS^{τ} denotes transition state and PC^{τ} denotes and product complex.

The O12...H9 intramolecular bond distance is approximately 1.58 Å in all media. The C1-C6-O9-H9 torsion angle is 0°, indicating that the H9 atom is on plane of the ring. The O13...H7 intermolecular hydrogen bond is longer than the O12...H9 intramolecular hydrogen bond in all the media. The C3...O13 intermolecular interaction is the longest. The molecular graph for $(RC^{\tau})_{add}$ is shown in Figure 4.24; $(RC^{\tau})_{add}$ is characterised by the presence of the O12...H9 and C10...O7 intramolecular bonds as well as the O13...H7 and C3...O13 intermolecular bonds. The O12...H9 bond forms part of a six member ring, the C10...O7 bond forms part of the five member ring, the O13...H7 bond and the C3...O13 bond form part of the five member ring. All the rings formed in $(RC^{\tau})_{add}$ can be identified by the ring critical points.

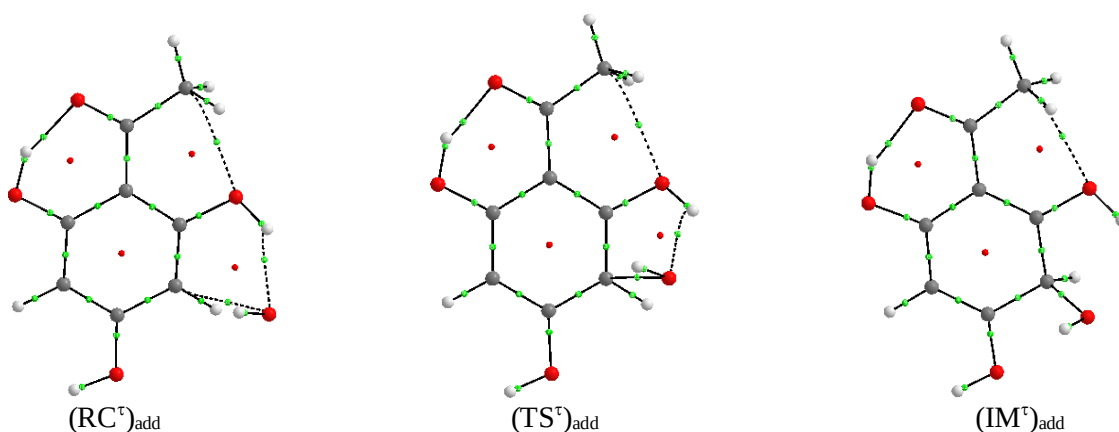


Figure 4.24: •OH addition reaction species molecular graphs for the THAP + •OH reaction, M06–2X/6-311++G(3df,2p) results *in vacuo*. The green dot within a given bond represents the bond critical point while the red dot within a given ring stands for the ring critical point.

The BCP data for the selected bonds in (RC[‡])_{add} are reported in Table 4.18; $\nabla\rho^2 > 0$ and $H < 0$ for the O12...H9 bond, indicating that the O12...H9 bond has a combination of strong and weak interaction characters in nature. The $\nabla\rho^2$ value and the H are all positive for the O13...H7 bond and the C3...O13 bond, implying that these bonds have weak interaction character in nature. The relative energy for (RC[‡])_{add} is reported in Table 4.19; (RC[‡])_{add} is approximately 5.752 kcal/mol lower than the sum of the energies of the separate reactant species, indicating that the THAP + •OH reaction may be initiated through the formation of (RC[‡])_{add} rather than directly from the isolated reactant species.

Table 4.18: M06–2X/6-311++G(3df, 2p) bond critical point properties for selected bonds within the reaction species obtained through the A-E mechanism that was performed without the inclusion of a catalyst and the oxidation mechanism that was performed without the inclusion of the O₂ molecule.

structure ^a and bond type	electron density ρ ($e\text{\AA}^3$)	Laplacian of the electron density $\nabla\rho^2$ ($e\text{\AA}^5$)	potential electron energy density V (Hartree)	kinetic electron energy density G (Hartree)	total electron energy density H (Hartree)
(RC ⁺) _{add}					
O12–H9	0.062818	0.153030	–0.066369	0.052313	–0.014060
O13···H7	0.019963	0.076357	–0.015926	0.017508	0.001582
C3···O13	0.020112	0.073904	–0.014299	0.016387	0.002088
(TS ⁺) _{add}					
O12–H9	0.064039	0.151538	–0.067718	0.052801	–0.014920
O13···H7	0.021059	0.083492	–0.017564	0.019219	0.001655
C3···O13	0.046232	0.127994	–0.035570	0.033785	–0.001790
(IM ⁺) _{add}					
O12–H9	0.052673	0.1505430	–0.053866	0.045751	–0.008120
C3–O13	0.248911	–0.5159330	–0.505084	0.188050	–0.317030
O7–H7	0.363199	–2.7649250	–0.826170	0.067470	–0.758700
C3–H3	0.281967	–1.0063050	–0.325021	0.036722	–0.288300
(TS ⁺) _{elim.}					
O12–H9	0.064425	0.166002	–0.060258	0.050879	–0.009380
O13···H7	0.224263	–0.877487	–0.380903	0.080766	–0.300140
C3···O13	0.154953	–0.010243	–0.198260	0.097850	–0.100410
O7···H7	0.107595	0.042758	–0.127257	0.068973	–0.058280
(TS ⁺) _{oxi}					
O12–H9	0.059384	0.152390	–0.062010	0.050054	–0.011960
O13···H7	0.022980	0.110881	–0.021116	0.024418	0.003302
C3–O13	0.281895	–0.495415	–0.700082	0.288114	–0.411970
C3···H3	0.058020	0.034316	–0.035928	0.022253	–0.013680
(PC ⁺) _{elim}					
O12–H9	0.061256	0.159344	–0.063815	0.051825	–0.011990
O13–H7	0.371407	–2.894503	–0.866161	0.071268	–0.794890
O13···H3	0.009235	0.037105	–0.006336	0.007806	0.001470
O7···H7	0.025816	0.092790	–0.020933	0.022065	0.001132
(PC ⁺) _{oxi}					
O12–H9	0.055278	0.158446	–0.056787	0.048199	–0.008590
C3–O13	0.293299	–0.444738	–0.799194	0.344005	–0.455190
C3···H3	0.017125	0.033795	–0.008742	0.008596	–0.000150

^aThe abbreviation TS stands for transition state, IM stands for intermedite and PC denotes product complex.

Table 4.19: Relative electronic energy (ΔE , kcal/mol), enthalpy (ΔH , kcal/mol) and Gibbs free energy (ΔG , kcal/mol) for THAP + $\bullet OH$ through the A-E mechanism performed without inclusion of the base and oxidation mechanism performed without inclusion of O_2 .

structure ^a	results obtained utilising the 6-31++G(d,p) basis set			results obtained utilising the 6-311++G(3df,2p) basis set		
	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative Gibbs free energy (ΔG , kcal/mol)	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative Gibbs free energy (ΔG , kcal/mol)
DFT/M06-2X results obtained <i>in vacuo</i>						
(R ⁺ +•OH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC ⁺) _{add}	-5.992	-6.363	1.807	-5.426	-5.752	2.228
(TS ⁺) _{add}	-4.913	-5.947	3.950	-4.700	-5.573	3.874
(IM ⁺) _{add}	-19.082	-20.129	-10.268	-18.806	-19.846	-9.963
(TS ⁺) _{elim}	2.673	0.922	12.234	3.584	1.905	13.075
(TS ⁺) _{oxi}	4.049	3.033	13.310	4.292	3.316	13.515
(PC ⁺) _{elim}	-34.510	-34.406	-27.799	-34.585	-34.483	-27.884
(P ⁺) _{oxi}	0.173	-0.380	8.829	0.270	-0.398	9.160
(P ⁺ +H ₂ O) _{iso}	-28.032	-27.775	-29.299	-29.026	-28.764	-30.270
(P ⁺ +•H) _{iso}	-1.192	-0.899	1.830	-0.941	-0.679	2.144
DFT/M06-2X results obtained in benzene solvent medium						
(R ⁺ +•OH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC ⁺) _{add}	-3.998	-4.290	3.744	-3.638	-3.862	3.901
(TS ⁺) _{add}	-3.162	-4.030	5.397	-3.084	-3.739	4.984
(IM ⁺) _{add}	-16.935	-17.925	-8.272	-16.874	-17.843	-8.223
(TS ⁺) _{elim}	4.077	2.381	13.551	4.840	3.214	14.202
(TS ⁺) _{oxi}	6.927	6.000	15.976	6.945	6.059	15.967
(PC ⁺) _{elim}	-33.157	-32.987	-26.535	-33.485	-33.290	-26.959
(P ⁺) _{oxi}	3.200	2.751	11.637	3.143	2.544	11.889
(P ⁺ +H ₂ O) _{iso}	-28.742	-28.431	-30.158	-29.565	-29.259	-30.941
(P ⁺ +•H) _{iso}	1.736	2.127	4.566	1.793	2.129	4.711
DFT/M06-2X results obtained in ethanol solvent medium						
(R ⁺ +•OH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC ⁺) _{add}	-3.649	-3.678	3.439	-4.054	-4.608	3.911
(TS ⁺) _{add}	-3.669	-3.990	3.581	-3.869	-3.990	3.581
(IM ⁺) _{add}	-16.636	-17.508	-7.893	-16.781	-17.681	-8.029
(TS ⁺) _{elim}	3.474	2.017	12.605	3.956	2.538	13.021
(TS ⁺) _{oxi}	8.934	7.977	18.170	8.501	7.613	17.649
(PC ⁺) _{elim}	-32.427	-32.175	-25.866	-32.702	-32.485	-26.128
(P ⁺) _{oxi}	5.304	4.935	13.753	4.605	4.160	13.147
(P ⁺ +H ₂ O) _{iso}	-30.472	-30.111	-31.905	-30.914	-30.564	-32.307
(P ⁺ +•H) _{iso}	3.779	4.438	5.584	3.426	3.926	6.097
DFT/MPW1K results obtained <i>in vacuo</i>						
(R ⁺ +•OH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC ⁺) _{add}	-3.520	-3.879	4.052	-2.947	-3.188	4.304
(TS ⁺) _{add}	-1.328	-2.363	7.506	-0.973	-1.928	7.707
(IM ⁺) _{add}	-15.402	-16.404	-6.719	-15.202	-16.153	-6.628
(TS ⁺) _{elim}	7.606	5.909	17.051	8.138	6.488	17.527
(TS ⁺) _{oxi}	9.919	8.949	19.063	9.240	8.296	18.328
(PC ⁺) _{elim}	-32.952	-32.855	-26.196	-32.879	-32.792	-26.082
(P ⁺) _{oxi}	6.660	6.711	14.163	5.800	5.840	13.230
(P ⁺ +H ₂ O) _{iso}	-28.088	-27.783	-29.447	-28.868	-28.549	-30.229
(P ⁺ +•H) _{iso}	4.831	5.122	7.792	4.101	4.394	7.056
DFT/MPW1K results obtained in benzene solvent medium						
(R ⁺ +•OH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC ⁺) _{add}	-1.398	-1.687	5.388	-0.892	-1.709	7.706
(TS ⁺) _{add}	0.620	-0.314	9.205	0.764	-0.104	9.306
(IM ⁺) _{add}	-13.181	-14.168	-4.549	-13.178	-14.108	-4.715
(TS ⁺) _{elim}	8.993	7.309	18.442	9.394	7.750	18.795
(TS ⁺) _{oxi}	12.930	11.973	22.000	12.010	11.083	21.010
(PC ⁺) _{elim}	-31.818	-31.578	-26.242	-31.884	-31.711	-25.634
(P ⁺) _{oxi}	9.869	9.906	17.533	8.698	8.782	15.989
(P ⁺ +H ₂ O) _{iso}	-28.566	-28.255	-29.977	-29.222	-28.901	-30.630
(P ⁺ +•H) _{iso}	7.836	8.184	10.663	6.879	7.211	9.723
DFT/MPW1K results obtained in ethanol solvent medium						
(R ⁺ +•OH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC ⁺) _{add}	-1.030	-0.906	5.637	-1.076	-0.857	5.181
(TS ⁺) _{add}	-0.719	-1.475	7.981	-0.810	-1.408	7.460
(IM ⁺) _{add}	-12.800	-13.718	-3.850	-13.053	-13.764	-4.666
(TS ⁺) _{elim}	8.129	6.698	17.268	8.191	7.004	16.700

(TS [‡]) _{oxi}	14.923	13.973	24.289	13.593	12.824	22.459
(PC [‡]) _{elim}	-31.223	-31.078	-24.412	-31.536	-31.043	-26.071
(P [‡]) _{oxi}	12.718	12.430	21.304	10.408	10.735	17.604
(P [‡] +H ₂ O) _{iso}	-30.084	-29.768	-31.265	-30.417	-30.093	-31.676
(P [‡] +•H) _{iso}	10.023	10.051	13.410	8.584	9.285	10.748
DFT/BHLLYP results obtained in vacuo						
(R [‡] +•OH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC [‡]) _{add}	-2.906	-3.223	4.499	-2.261	-2.497	4.632
(TS [‡]) _{add}	1.808	0.816	10.610	2.288	1.353	10.988
(IM [‡]) _{add}	-10.806	-11.783	-2.145	-10.388	-11.319	-1.806
(TS [‡]) _{elim}	14.268	12.629	23.601	15.110	13.520	24.388
(TS [‡]) _{oxi}	14.841	13.814	24.058	14.426	13.435	23.577
(PC [‡]) _{elim}	-32.404	-32.299	-25.669	-32.388	-32.230	-25.949
(P [‡]) _{oxi}	11.681	11.582	19.782	10.996	10.885	19.131
(P [‡] +H ₂ O) _{iso}	-27.293	-27.001	-28.619	-28.040	-27.741	-29.361
(P [‡] +•H) _{iso}	10.388	10.661	13.388	9.682	9.947	12.690
DFT/BHLLYP results obtained in benzene solvent medium						
(R [‡] +•OH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC [‡]) _{add}	-0.882	-1.719	7.785	-0.404	-1.169	8.149
(TS [‡]) _{add}	3.598	2.672	12.254	3.886	2.999	12.519
(IM [‡]) _{add}	-8.683	-9.635	-0.145	-8.416	-9.332	0.063
(TS [‡]) _{elim}	15.523	13.901	24.844	16.245	14.669	25.492
(TS [‡]) _{oxi}	17.814	16.798	26.957	17.160	16.185	26.226
(PC [‡]) _{elim}	-31.437	-31.184	-25.777	-31.408	-31.223	-25.250
(P [‡]) _{oxi}	14.871	14.765	23.035	13.924	13.841	21.982
(P [‡] +H ₂ O) _{iso}	-27.856	-27.561	-29.238	-28.464	-28.169	-29.826
(P [‡] +•H) _{iso}	13.244	13.575	16.090	12.474	12.778	15.358
DFT/BHLLYP results obtained in ethanol solvent medium						
(R [‡] +•OH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC [‡]) _{add}	-0.790	-0.665	5.925	-0.773	-0.662	5.976
(TS [‡]) _{add}	1.874	1.140	10.373	2.032	1.257	10.605
(IM [‡]) _{add}	-8.669	-9.497	-0.034	-8.562	-9.395	0.043
(TS [‡]) _{elim}	14.081	12.252	23.637	14.642	12.827	24.181
(TS [‡]) _{oxi}	19.559	18.615	28.724	2.032	1.257	10.605
(PC [‡]) _{elim}	-31.141	-30.938	-24.559	-31.355	-31.039	-25.353
(P [‡]) _{oxi}	17.347	17.078	25.855	15.444	15.570	23.179
(P [‡] +H ₂ O) _{iso}	-29.748	-29.382	-31.174	-30.010	-29.651	-31.415
(P [‡] +•H) _{iso}	15.508	15.996	18.204	14.047	14.654	16.107

^aThe abbreviation R[‡]_{iso} stands for isolated reactant species, RC[‡]_{add} stands for reactant complex, TS[‡] denotes transition state, IM[‡] denotes intermediate species, PC[‡]_{add} stands for product complex and P[‡]_{iso} denotes isolated product species respectively. Subscript “elim” in the TS and PC represent reaction species obtained through the A-E mechanism while subscript “oxi” in the TS and PC represent reaction species obtained through oxidation mechanism.

The scan for the C3...O13 bond was performed with the aim of adding •OH to THAP in (RC[‡])_{add}; it is shown in Figure 4.25; it is characterised by a minimum point located at the C3...O13 bond distance of 2.603 Å, another minimum point located at the C3...O13 bond distance of 1.403 Å and a maximum point located at the C3...O13 bond distance of 2.003 Å. Optimisation followed by frequency calculations on the individual structures found at the two minima points gave zero imaginary frequencies while the structure at the maximum point gave one imaginary frequency. The structure found at the first minimum is actually (RC[‡])_{add}, the structure obtained at the second minimum is the intermediate species; it is denoted throughout the work as (IM[‡])_{add}. The structure found at the maximum point corresponds to the transition state; it is denoted as (TS[‡])_{add}. The magnitude (cm⁻¹) of the imaginary frequency for the stretching of the C3...O13 bond in (TS[‡])_{add} is 122 in *vacuum* medium, 183 in benzene solvent medium and 151 in ethanol

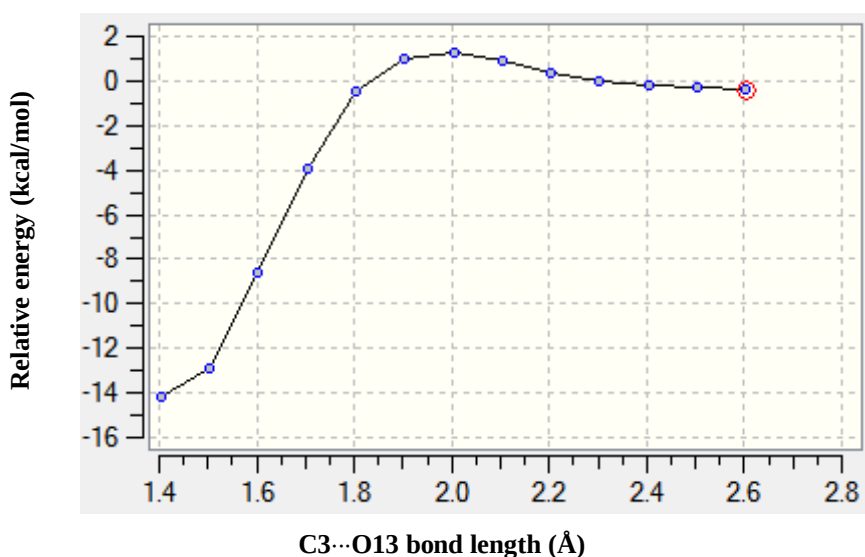


Figure 4.25: M06–2X/6-31+G(d, p) results *in vacuo* corresponding to the C3...O13 bond scan (in steps of 0.1 Å) for the addition of •OH to the THAP molecule to form an intermediate species.

solvent medium. The geometry as well as some selected bond lengths for $(TS^\ddagger)_{add}$ and $(IM^\ddagger)_{add}$ are shown in Figure 4.23; their corresponding molecular graphs are shown in Figure 4.24. Their electronic properties at BCPs are reported in Table 4.18 while the energetic properties are reported in Table 4.19. $(TS^\ddagger)_{add}$ is characterised by the elongation of the O13...H7 bond and the shortening of the C3...O13 bond in comparison with their respective values in $(RC^\ddagger)_{add}$. There is minimal difference between the C12...H9 bond distance in $(TS^\ddagger)_{add}$ and in $(RC^\ddagger)_{add}$.

The molecular graph for $(TS^\ddagger)_{add}$ shows the presence of the O12...H9 bond, the C10...O7 bond, the O13...H7 bond and the C3...O13 bond. The ρ value for the O12...H9 bond shows no significant variation with its respective value in $(RC^\ddagger)_{add}$, implying that the accumulation of the electron density within the O12...H9 bond is independent of the geometry change of the reaction species. The $\nabla^2\rho$ value is positive while the H value is negative for the O12...H9 bond, suggesting that the O12...H9 bond is characterised by both the strong and weak interactions. O13...H7 and C3...O13 bonds have higher value

of ρ in $(TS^\ddagger)_{\text{add}}$ than in $(RC^\ddagger)_{\text{add}}$, suggesting that more electrons are accumulated within the O13...H7 bond and the C3...O13 bond in $(TS^\ddagger)_{\text{add}}$ than in $(RC^\ddagger)_{\text{add}}$. The $\nabla^2\rho$ value and the H value are all positive for the O13... H7 bond while $\nabla^2\rho > 0$ and $H < 0$ for the C3...O13 bond, implying that the O13...H7 bond has weak interaction character while C3...O13 has both weak and strong interaction characters in nature.

The structure for $(IM^\ddagger)_{\text{add}}$ shows the existence of the covalent bond between C3 and O13. The molecular graph for $(IM^\ddagger)_{\text{add}}$ confirms the presence of the C3–O13 bond. The electronic properties at BCPs for $(IM^\ddagger)_{\text{add}}$ are also reported in Table 4.18; the $\nabla^2\rho$ value and the H value are all negative for the C3–O13 bond, indicating that the C3–O13 bond is strong in nature.

The ΔE_{act} (kcal/mol) value for the addition step is 0.726 *in vacuo*, 0.778 in benzene and 0.185 in ethanol, implying that the change in the dielectric constant of the media has minimal effect on the barrier height of the reaction through the $\bullet\text{OH}$ addition step. The reaction rate constant associated with the $\bullet\text{OH}$ addition step is reported in Table 4.20; it is denoted as $k^\ddagger_{\text{add}}$. The $k^\ddagger_{\text{add}}$ value is to the order of the magnitude $10^{11} \text{ M}^{-1} \text{ s}^{-1}$, which corresponds to the diffusion controlled type of a reaction.

Table 4.20: Reaction rate constants for the different mechanisms associated with the THAP + •OH reaction

calculation method	results with the 6-31++G(d,p) basis set			results with the 6-311++G(3df,2p) basis set		
	<i>in vacuo</i>	in benzene	in ethanol	<i>in vacuo</i>	in benzene	in ethanol
estimated rate constant associated with the •OH addition to the ring (k^{τ}_{add} , M ⁻¹ s ⁻¹)						
DFT/M06–2X	1.580×10 ¹¹	3.617×10 ¹¹	1.561×10 ¹¹	3.660×10 ¹¹	9.453×10 ¹¹	3.370×10 ¹¹
DFT/MPW1K	1.729×10 ¹⁰	9.372×10 ⁹	1.127×10 ¹¹	1.886×10 ¹⁰	3.954×10 ¹¹	1.258×10 ¹¹
DFT/BHHLYP	1.950×10 ⁸	3.122×10 ⁸	3.229×10 ⁹	1.290×10 ⁸	3.686×10 ⁹	2.380×10 ⁹
estimated rate constant (k^{τ}_{elim} , (s ⁻¹)) associated with the H ₂ O elimination in the addition-elimination reaction performed without inclusion of the base						
DFT/M06–2X	1.882×10 ⁻⁴	5.920×10 ⁻⁴	5.544×10 ⁻³	7.617×10 ⁻⁵	2.141×10 ⁻⁴	2.185×10 ⁻³
DFT/MPW1K	2.215×10 ⁻⁵	8.256×10 ⁻⁵	1.947×10 ⁻³	1.155×10 ⁻⁵	3.435×10 ⁻⁵	1.281×10 ⁻³
DFT/BHHLYP	7.879×10 ⁻⁷	2.832×10 ⁻⁶	2.619×10 ⁻⁵	3.703×10 ⁻⁷	1.345×10 ⁻⁶	1.191×10 ⁻⁵
estimated rate constant ($k^{\tau}_{\text{elim, base}}$, (s ⁻¹)) associated with the •OH elimination for the addition-elimination reaction performed with inclusion of the base ^a						
DFT/BHHLYP ^a	— ^b	6.494×10 ³	1.423×10 ⁶	— ^b	9.172×10 ³	1.011×10 ⁶
estimated rate constant (k^{τ}_{oxi} , (s ⁻¹)) associated with the •H elimination step in the oxidation reaction performed without inclusion of O ₂						
DFT/M06–2X	3.064×10 ⁻⁵	9.874×10 ⁻⁶	4.620×10 ⁻⁷	3.622×10 ⁻⁵	1.088×10 ⁻⁵	8.843×10 ⁻⁷
DFT/MPW1K	7.418×10 ⁻⁷	2.033×10 ⁻⁷	1.388×10 ⁻⁸	2.989×10 ⁻⁶	8.168×10 ⁻⁷	7.697×10 ⁻⁸
DFT/BHHLYP	3.644×10 ⁻⁷	7.996×10 ⁻⁸	4.886×10 ⁻⁸	1.455×10 ⁻⁶	3.896×10 ⁻⁷	5.886×10 ⁻⁸
estimated rate constants associated with the oxidation mechanism performed with the inclusion of the O ₂ molecule						
estimated rate constant (k^{τ}_{1,O_2} , (s ⁻¹)) associated with the addition of O ₂ to acylated tetrahydroxycyclohexadienyl peroxy radical						
DFT/M06–2X	1.825×10 ¹¹	1.125×10 ¹⁰		7.354×10 ¹⁰	— ^c	
DFT/MPW1K	3.597×10 ⁸	— ^d		2.632×10 ⁸	— ^d	
DFT/BHHLYP	1.169×10 ⁷	1.168×10 ⁷		4.028×10 ⁶	4.027×10 ⁶	
estimated rate constant (k^{τ}_{2,O_2} , (s ⁻¹)) associated with the elimination of the OOH radical						
DFT/M06–2X	8.925×10 ⁶	1.409×10 ⁷		1.327×10 ⁷	2.959×10 ⁷	
DFT/MPW1K	1.411×10 ⁷	1.419×10 ⁷		2.967×10 ⁷	2.385×10 ⁷	
DFT/BHHLYP	5.606×10 ⁵	1.743×10 ⁷		1.023×10 ⁶	1.204×10 ⁷	
estimated rate constant, k^{τ}_{3,O_2} , (s ⁻¹) for the isomerisation of acylated trihydroxycyclohexadienone anion radical to form acylated tetrahydroxybenzene						
DFT/M06–2X	1.453×10 ⁻²⁹	2.773×10 ⁻²⁸		1.346×10 ⁻²⁹	1.307×10 ⁻²⁸	
DFT/MPW1K	1.565×10 ⁻³²	4.255×10 ⁻³⁹		6.029×10 ⁻³²	5.868×10 ⁻³¹	
DFT/BHHLYP	1.492×10 ⁻²⁸	1.173×10 ⁻³³		2.291×10 ⁻³³	6.219×10 ⁻³⁴	

^a The •OH elimination reaction was only achieved using the DFT/BHHLYP calculation method.

^b The •OH elimination reaction can only be envisaged to occur in the presence of solvent molecules.

^c On optimisation, the geometry obtained did not corresponding to the desired intermediate structure, as such the rest of the calculations were not meaningful to calculate

^d On optimisation the transition state structure could not be obtained.

4.4.2 Dehydration step associated with the A-E mechanism

The intermediate species (acylated tetrahydroxycyclohexadienyl radical) obtained in section 4.4.1 can undergo dehydration to form a phenoxyl radical species. The dehydration step was performed under neutral and basic conditions. The study in basic environment was performed with the objective of catalysing the reaction in a similar manner to what was done in the case of the $\text{FG} + \bullet\text{OH}$ reaction (section 4.3.3).

4.3.2.1 Dehydration step performed without inclusion of a base

In the absence of the catalyst, the reaction is thought to proceed in such a manner that the H7 atom is transferred to the O13 atom. In this way, the dehydration of $(\text{IM}^\ddagger)_{\text{add}}$ was achieved by performing a $\text{O13}\cdots\text{H7}$ bond scan with the objective of eliminating H7 from O7 and attaching it to O13; the outcome of the scan is shown in Figure 4.26. The plot has a minimum point at the $\text{O13}\cdots\text{H7}$ bond distance of 2.150 Å and another minimum at $\text{O13}\cdots\text{H7}$ bond distance of 0.950 Å. The structure found at either of the minimum was optimised separately. Frequency calculation was then performed on the optimised structure. The results of the frequency calculations gave zero imaginary frequencies on each case, which suggest that the two structures are true minima on the potential energy surface. The structure at the minimum corresponding to the $\text{O13}\cdots\text{H7}$ bond distance of 2.150 Å is actually $(\text{IM}^\ddagger)_{\text{add}}$ while the structure at the $\text{O13}\cdots\text{H7}$ bond distance of 0.950 Å is the product complex, comprising of the interacting phenoxyl radical and a water molecule; it is denoted as $(\text{PC}^\ddagger)_{\text{elim}}$. The structure at the maximum point is located at the $\text{O13}\cdots\text{H7}$ bond distance of 1.150 Å; it was separately optimised and then frequency calculation was performed on the optimised geometry (using the same basis set as was utilised during optimisation). The outcome of the frequency calculation gave one imaginary frequency (the magnitude of the imaginary frequency is 797 *in vacuum* medium, 766 in benzene solvent medium and 679 in ethanol solvent medium), suggesting that the structure at the maximum corresponds to a transition state. It is denoted throughout this work as $(\text{TS}^\ddagger)_{\text{elim}}$. The geometry of both $(\text{TS}^\ddagger)_{\text{elim}}$ and $(\text{PC}^\ddagger)_{\text{elim}}$, along with some selected bond lengths, and corresponding molecular graphs are shown in Figure 4.27; their electronic properties at BCPs are included in Table 4.18 while the energetic properties are included in Table 4.19.

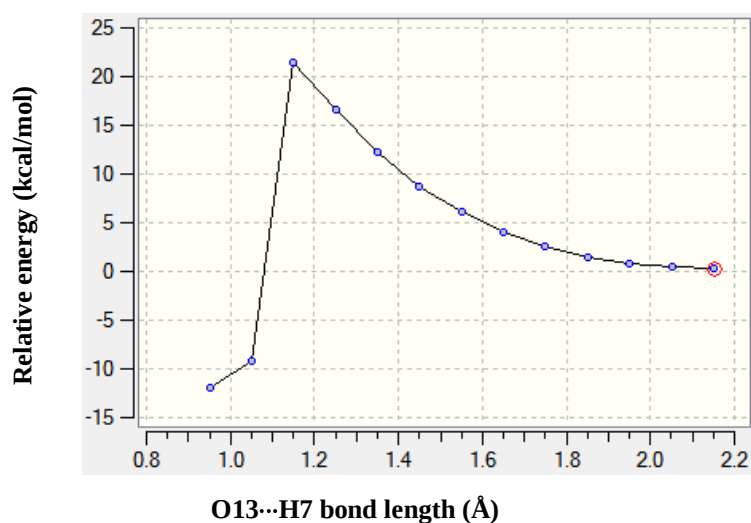


Figure 4.26: M06–2X/6-31+G(d, p) results *in vacuo* corresponding to the O13...H7 bond scan (in steps of 0.1 Å) for the dehydration step in the absence of a catalyst.

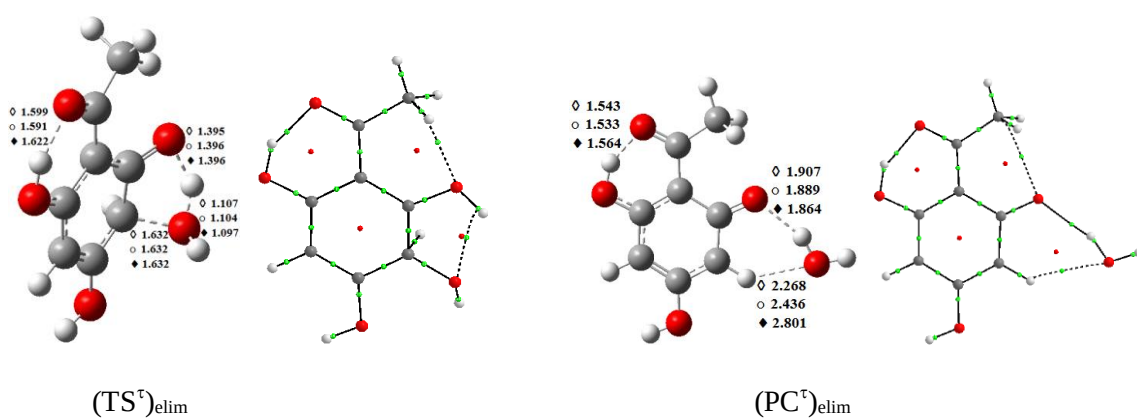


Figure 4.27: M06–2X/6-311++G(3df,2p) geometries and corresponding molecular graphs for transition state ((TS[‡])_{elim}) and product complex ((PC[‡])_{elim}) associated with the dehydration step in the A-E mechanism performed without inclusion of the base. The bond lengths shown on each geometry are those corresponding to the results *in vacuo* (◇), in benzene (○) and in ethanol (◆) media. The green dot within a given bond represents the bond critical point while the red dot within a given ring stands for ring critical point.

The C3...O13 bond distance in the geometry for (TS[‡])_{elim} is longer than the value it has in the geometry for (IM[‡])_{add}, indicating that the C3...O13 bond is inclining towards breaking while the O13–H7 is tending towards forming. (TS[‡])_{elim} has longer O7–H7 bond than (IM[‡])_{add}, indicating that the O7–H7 bond elongates in the geometry for (TS[‡])_{elim} with respect to its value in the geometry for (IM[‡])_{add}. (TS[‡])_{elim} has a shorter O12...H9 bond than the value it has in the geometry for (IM[‡])_{add}. C3...O13 and O7...H7 bonds have lower value of ρ in the geometry for (TS[‡])_{elim} than in the geometry for (IM[‡])_{add}, suggesting that the two bonds are weaker in the geometry for (TS[‡])_{elim} than in the geometry for (IM[‡])_{add}; these results are in agreement with the analysis of the C3...O13 and O7–H7 bond distances in the two structures. The electron density value for the C3...H7 bond increases from (IM[‡])_{add} to (TS[‡])_{elim}, suggesting that the C3...H7 bond is stronger in (TS[‡])_{elim} than in (IM[‡])_{add}. The $\nabla^2\rho$ and the H values for the C3...O13 bond and for the O13...H7 bond are all negative. These results agrees with the analysis of both hydrogen bond length and electron density distribution in that they indicate that the C3...O13 bond and the O13...H7 bond are shared type of interactions in nature. The $\nabla^2\rho$ value is positive and the H is negative for O7...H7, suggesting that it has a mixture of weak and strong interaction characters in nature. This is also confirmed by the $|V|/G$ ratio for the O7...H7 bond.

(PC[‡])_{elim} is characterised by the O7...H7 intermolecular interaction between phenoxyl radical and a water molecule, in which the water molecule is the hydrogen bond donor and the phenoxyl radical is the hydrogen bond acceptor. The O7...H7 intermolecular interaction is easily identifiable in the molecular graph for (PC[‡])_{elim}; (PC[‡])_{elim} is also characterised by the existence of the weak O13...H3–C3 hydrogen bond (which can be identified through analysis of the bond length parameters; the O13...H3–C3 bond length parameters in different media are characteristics of a weak hydrogen bond), which forms part of the six member ring; in total, (PC[‡])_{elim} has four six member rings (including the original benzene ring), which contributes to its stabilisation as an adduct structure. The electronic properties for (PC[‡])_{elim} at BCPs are also reported in Table 4.18; the O13–H7 bond has higher electron density within the geometry of (PC[‡])_{elim} than within the geometry of (TS[‡])_{elim}. The $\nabla^2\rho$ value and the H value for the O7...H7–O13 and

O13...H3–C3 hydrogen bonds are all positive, indicating that the O7...H7–O13 hydrogen bond and the O13...H3–C3 hydrogen bond are weak in nature.

The energy profile for the overall mechanism is shown in Figure 4.28. The ΔE_{act} (kcal/mol) value is 22.390 *in vacuo*, 21.714 in benzene and 20.737 in ethanol, indicating that the barrier height for the dehydration step is significantly higher than for the $\bullet\text{OH}$ addition mechanism. In this way, the dehydration step controls the rate of the overall A-E mechanism.

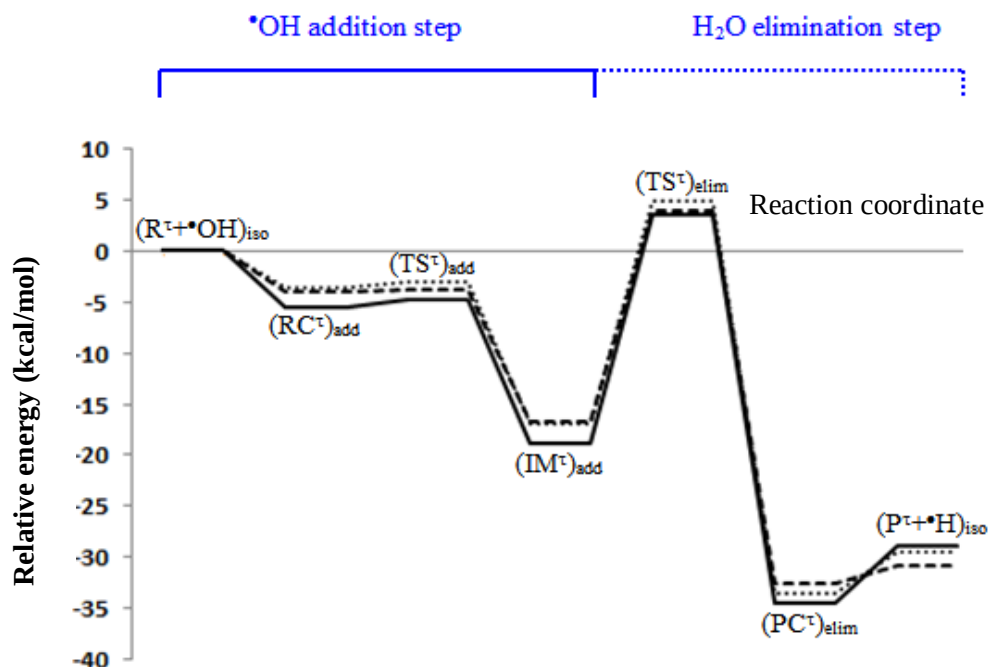


Figure 4.28: M06–2X/6-311++G(3df,2p) energy profile (potential energy versus reaction coordinate) for the reaction of THAP + $\bullet\text{OH}$ through the A-E mechanism performed without addition of a catalyst; results *in vacuo* (—), in benzene (.....) and in ethanol (-----) media.

The enthalpy of $(PC^{\tau})_{\text{elim}}$ is significantly lower than the enthalpy of $(RC^{\tau})_{\text{add}}$, implying that $\text{THAP} + \bullet\text{OH}$ through the A-E mechanism is exothermic and thermodynamically favoured. The ΔG value between $(PC^{\tau})_{\text{elim}}$ and $(RC^{\tau})_{\text{add}}$ is negative, so that $\text{THAP} + \bullet\text{OH}$ can be considered to be spontaneous in nature.

The rate constant for the dehydration step associated with the A-E mechanism performed without inclusion of the base is reported in Table 4.20 and it is denoted as k^{τ}_{elim} ; it is to the order of magnitude (s^{-1}) 10^{-4} – 10^{-3} in different media. The k^{τ}_{elim} value obtained for $\text{THAP} + \bullet\text{OH}$ is consistent with the high reaction barrier obtained from the analysis of the energetic values. A comparison of the k^{τ}_{elim} value and the k^{τ}_{add} value suggests that the k^{τ}_{elim} value is significantly smaller than the k^{τ}_{add} value, informing that the dehydration step is likely to occur slower than the $\bullet\text{OH}$ addition step. In this way, should the A-E mechanism proceed in the absence of a base, the water elimination step would be the rate-limiting step for the overall mechanism.

4.3.2.2 Dehydration step for A-E mechanism with inclusion of a base catalyst

The dehydration of $(IM^{\tau})_{\text{add}}$ (obtained in section 4.4.1) in the presence of a base catalyst requires the abstraction of H7 in $(IM^{\tau})_{\text{add}}$ by the OH^{-} catalyst to form an acylated trihydroxycyclohexadienone anion radical (and a water molecule) and a subsequent elimination of OH^{-} from trihydroxycyclohexadienone anion radical to form a stable phenoxyl radical and OH^{-} . The dehydration step performed with the inclusion of the base is represented by subscript “elim, base”. We denote in this dissertation the oxygen atom and the hydrogen atom of the hydroxyl anion as O14 and H14, respectively.

The first step involves the interaction of $(IM^{\tau})_{\text{add}}$ and OH^{-} , which results in a rapid proton abstraction, forming an intermediate species that is made up of acylated trihydroxycyclohexadienone anion radical and a water molecule. Acylated trihydroxycyclohexadienone anion radical is denoted as $(IM^{\tau})_{\text{base,elim}}$. The O14...H7 reverse bond scan (Figure 4.29) was performed starting from $(IM^{\tau})_{\text{base,elim}}$ to yield $(IM^{\tau})_{\text{add}}$ and OH^{-} . The outcome of the scan shows no reaction barrier, indicating that the proton abstraction from $(IM^{\tau})_{\text{add}}$ by OH^{-} is a rapid process.

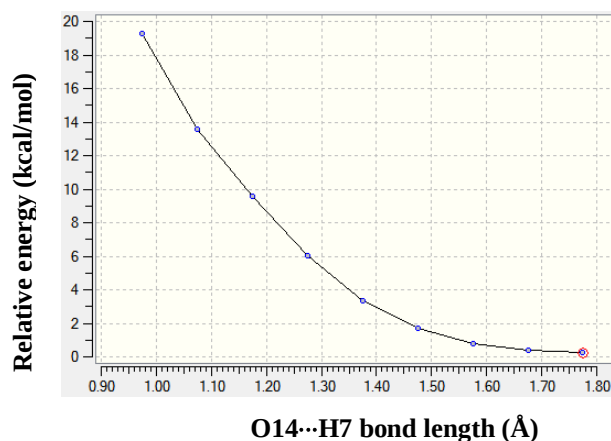


Figure 4.29: BHHLYP/6-31+G(d, p) O14...H7 bond scan (in steps of 0.1 Å) performed in ethanol for the abstraction of H7 by OH⁻

The geometry of (IM[‡])_{base,elim}, together with its selected geometric properties, and the corresponding molecular graph are shown in Figure 4.30; Table 4.20 reports the electronic properties at the bond critical points. (IM[‡])_{base,elim} is characterised by the presence of the carbonyl group, which gives the structure the phenoxy character. The C4–C3–O13–H13 torsion angle (°) has a value of –55 and –57 in benzene and in ethanol, respectively; implying that the H13 atom is off plane; it is also characterised by the presence of the C12...H9 and C3–O13 bonds. The $\nabla^2\rho$ value and the H value are all negative for the C3–O13 bond and for the C2...O7 bond, indicating that the C3–O13 bond and the C2...O7 bond are covalent in nature.

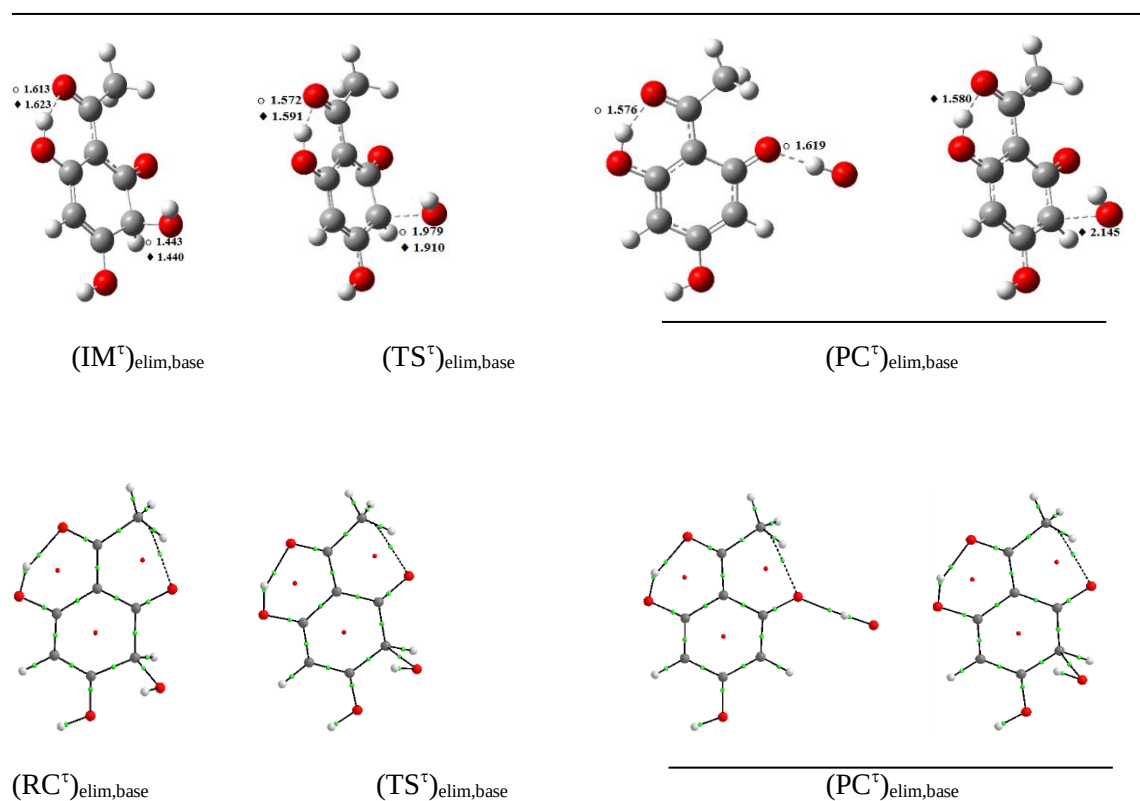


Figure 4.30: BHLYP/6-311++G(3df,2p) geometries (first row) and their corresponding molecular graphs (second row) for the reaction species involved in the elimination of OH^- from acylated trihydroxycyclohexadienone anion radical. The bond lengths in the reaction species are obtained in benzene ($\circ$) and in ethanol ($\blacklozenge$) media. The first $(\text{PC}^\ddagger)_{\text{elim,base}}$ on the left is obtained in benzene while the second $(\text{PC}^\ddagger)_{\text{elim,base}}$ on the right is obtained in ethanol. The green dot within a given bond represents the bond critical point while the red dot within a given ring stands for the ring critical point.

Table 4.21: BHHLYP/6-311++G(3df, 2p) bond critical point properties for selected bonds within the reaction species obtained through the OH⁻ elimination step for the THAP + •OH reaction performed with inclusion of the base.

structure ^a and bond type	electron density ρ ($e\text{\AA}^3$)	Laplacian of the electron density $\nabla\rho^2$ ($e\text{\AA}^5$)	potential electron energy density V (Hartree)	kinetic electron energy density G (Hartree)	total electron energy density H (Hartree)
BHHLYP/6-311++G(3df, 2p) results obtained in the presence of the benzene solvent medium					
(IM [•]) _{elim,base}					
O12–H9	0.055918	0.154632	–0.058056	0.048502	–0.00955
C2–O7	0.400061	–0.500753	–1.322903	0.598007	–0.72490
C3–O13	0.370967	–2.947747	–0.883941	0.072732	–0.81121
(TS [•]) _{elim,base}					
O12–H9	0.060552	0.159717	–0.064194	0.052036	–0.01216
C2–O7	0.397194	–0.566465	–1.293271	0.575602	–0.71767
C3–O13	0.087157	0.133084	–0.076594	0.055057	–0.02154
(PC [•]) _{elim,base}					
O12–H9	0.062716	0.162167	–0.065943	0.053242	–0.01270
C2–O7	0.387986	–0.660968	–1.214234	0.524496	–0.68974
O7–H13	0.051344	0.139632	–0.048922	0.041915	–0.00701
BHHLYP/6-311++G(3df, 2p) results obtained in the presence of the ethanol solvent medium					
(IM [•]) _{elim,base}					
O12–H9	0.056918	0.155632	–0.058156	0.048532	–0.00962
C2–O7	0.401061	–0.510753	–1.323903	0.598107	–0.72580
C3–O13	0.380967	–2.957747	–0.884941	0.072752	–0.81219
(TS [•]) _{elim,base}					
O12–H9	0.061552	0.160717	–0.064294	0.052236	–0.01206
C2–O7	0.398194	–0.567465	–1.293471	0.575802	–0.71767
C3–O13	0.088157	0.134084	–0.076794	0.055157	–0.02164
(PC [•]) _{elim,base}					
O12–H9	0.063262	0.161870	–0.066533	0.053500	–0.01303
C2–O7	0.399516	–0.577951	–1.297906	0.576709	–0.72120
C3–O13	0.003977	0.120673	–0.039865	0.035016	0.00485

^aIM[•] stands for the intermediate species, TS[•] stands for the transition state and PC[•] denotes the product complex. The subscripts “elim base” denotes water elimination step with inclusion of a base catalyst.

The OH⁻ elimination step was achieved by performing the C3–O13 bond scan in (IM[•])_{base,elim} with the purpose of forming the phenoxyl radical and a water molecule. Figure 4.31 presents the results of the scan; the graph is characterised by the minimum point at the C3–O13 bond distance of 1.449 Å, the minimum point at the C3–O13 bond distance of 2.449 Å and the maximum point at the C3–O13 bond distance of 1.949 Å. All the three structures found at the stationary points were separately optimised. Frequency calculations were then run on the optimised structures in order to determine the nature of the stationary points. Both minima points gave zero imaginary frequencies while the maximum point gave one imaginary frequency of magnitude (cm⁻¹) 272 and 319 in

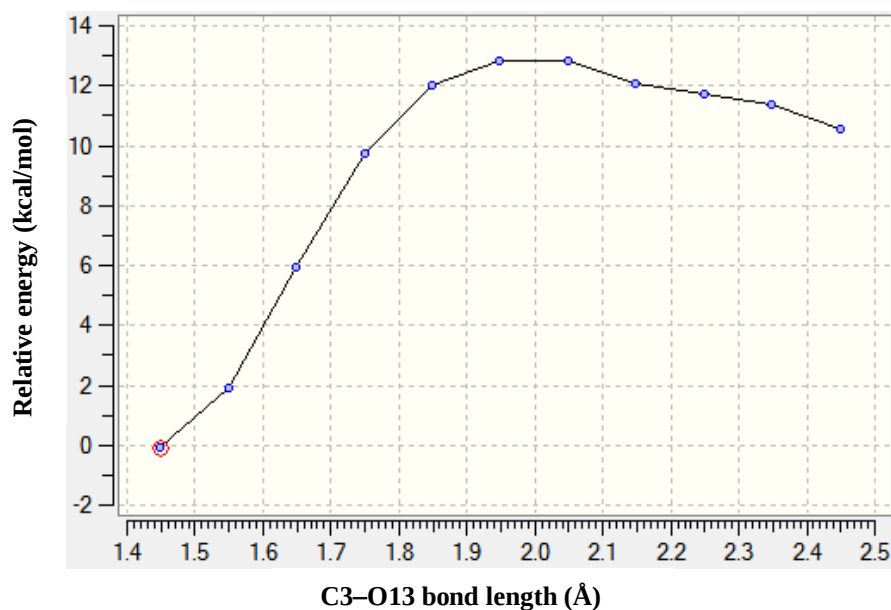


Figure 4.31: BHHLYP/6-31+G(d, p) scan for the C3–O13 bond (in steps of 0.1Å) for the purpose of elimination of OH[−] in order to form the phenoxyl radical. The scan was performed the presence of the ethanol solvent medium.

benzene and in ethanol, respectively. The implication of this finding is that both minima are true minima on the potential energy surface while the maximum point corresponds to a transition state on a potential surface. The minimum point at C3–O13 bond distance of 1.449 Å is (IM[‡])_{base,elim}, the minimum point at the C3–O13 bond distance of 2.449 Å is the product complex, which is denoted as (PC[‡])_{base,elim}. The transition state found at the C3–O13 bond distance of 1.949 Å is denoted as (TS[‡])_{base,elim}. The geometries of (TS[‡])_{base,elim} and (PC[‡])_{base,elim} (along with their selected geometric properties) as well as their corresponding molecular graphs are also shown in Figure 4.30, while their electronic properties are reported in Table 2.25; (TS[‡])_{base,elim} has longer C3–O13 bond than (IM[‡])_{base,elim}. The C3–O13 bond has lower ρ value in the geometry of (TS[‡])_{base,elim} than in the geometry of (IM[‡])_{base,elim}, indicating that electrons are less accumulated within the C3–O13 bond in (TS[‡])_{base,elim} than in (IM[‡])_{base,elim}, which explains the fact that (TS[‡])_{base,elim} has longer C3–O13 bond than (IM[‡])_{base,elim}. The C3–O13 bond in (TS[‡])_{base,elim} has positive value of $\nabla^2\rho$ and negative value of H , implying that it can be described as possessing both

strong and weak interaction characters in nature. The O12–H9 bond is slightly longer in $(\text{TS}^\ddagger)_{\text{base,elim}}$ than in $(\text{IM}^\ddagger)_{\text{base,elim}}$, indicating that it is minimally affected by the change in geometry of the reaction species. The geometry of $(\text{PC}^\ddagger)_{\text{base,elim}}$ is different in benzene and in ethanol. $(\text{PC}^\ddagger)_{\text{base,elim}}$ in benzene has the O7...H13 intermolecular hydrogen bond between phenoxyl and the ^-OH anion while it has the C3...O10 intermolecular bond in ethanol. The electronic parameter of $(\text{PC}^\ddagger)_{\text{base,elim}}$ at BCPs are reported in Table 4.21; The results suggest that $\nabla^2\rho > 0$ while $H < 0$ for the O7...H13 bond in benzene, indicating that the O7...H13 bond has a mixture of strong interactions and weak interaction characters in nature. However, analysis of the $|V|/G$ value indicates that it is more of a weak bond than a strong bond. The $\nabla^2\rho$ and H values are positive for the C3...O10 bond in ethanol, indicating that the C3...O10 bond is weak in nature; a fact that is also confirmed by the $|V|/G$ value, which is 1.1.

The overall energy profile for the THAP + $^{\bullet}\text{OH}$ reaction (including all the three steps) in the presence of a base is shown in Figure 4.32 while the energies for the reaction species are reported in Table 4.22. The ΔE_{act} (kcal/mol) value for the OH^- elimination step is 11.596 in benzene and 9.169 in ethanol, indicating that ΔE_{act} is higher in non-polar medium than in polar medium. The OH^- elimination step has higher ΔE_{act} than the $^{\bullet}\text{OH}$ addition step, which implies that it is the rate-limiting step for the overall A-E mechanism when performed with inclusion of a base catalyst. The difference in the ΔE_{act} values for the dehydration step performed with inclusion of a base and that performed without inclusion of the base suggests that the A-E mechanism is preferred in basic environment to neutral environment. The ΔG value between $(\text{PC}^\ddagger)_{\text{base,elim}}$ and $(\text{RC}^\ddagger)_{\text{add}}$ is less than zero, implying that the THAP + $^{\bullet}\text{OH}$ reaction performed with inclusion of base medium is spontaneous. The enthalpy of $(\text{PC}^\ddagger)_{\text{base,elim}}$ is significantly lower than that of $(\text{RC}^\ddagger)_{\text{add}}$, suggesting that THAP + $^{\bullet}\text{OH}$ reaction performed within the basic medium is exothermic in polar and in non-polar media. The change in enthalpy between the $(\text{PC}^\ddagger)_{\text{base,elim}}$ and $(\text{RC}^\ddagger)_{\text{add}}$ is smaller in benzene than in ethanol, informing that the reaction is more favoured in non-polar medium than in polar medium.

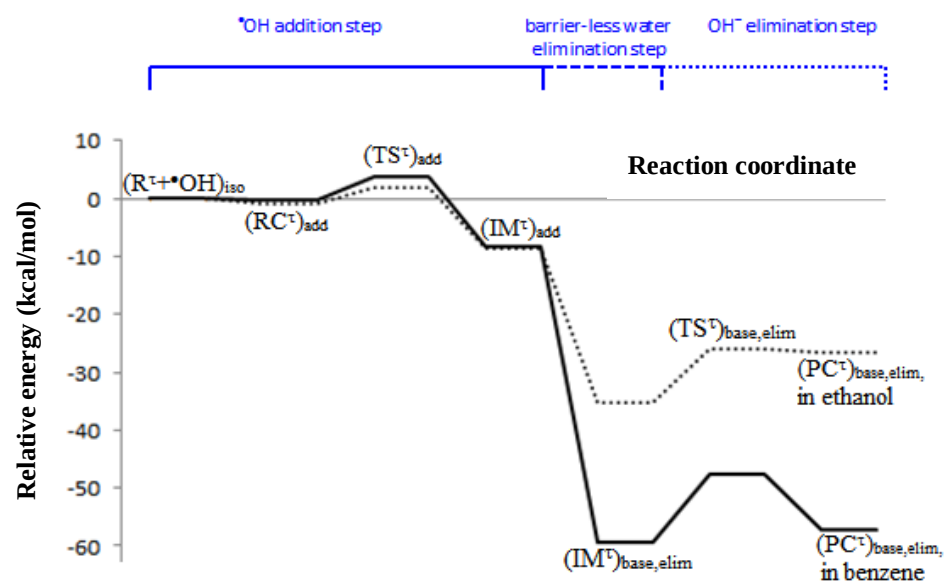


Figure 4.32: BHHLYP/6-311++G(3df, 2p) energy profile (potential energy versus reaction coordinate) for the THAP + $\bullet OH$ reaction through the A-E mechanism performed with inclusion of a catalyst. Results in benzene (—) and in ethanol (.....) media.

Table 4.22: Relative electronic energy (ΔE , Hartree), relative enthalpy (ΔH , Hartree), relative Gibbs free energy (ΔG , Hartree) and entropy (S, cal/mol. K) for the THAP with $\bullet\text{OH}$ reaction species obtained from dehydration step of the A-E mechanism performed in basic medium.

structure ^a	results obtained with the 6-31++G(d,p) basis set			results obtained with the 6-311++G(3df,2p) basis set		
	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative Gibbs free energy (ΔG , kcal/mol)	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative Gibbs free energy (ΔG , kcal/mol)
DFT/BHHLYP results in benzene solvent medium						
(IM [•]) _{elim, base}	0.000	0.000	0.000	0.000	0.000	0.000
(TS [•]) _{elim, base}	11.642	11.476	12.219	11.596	11.449	12.015
(PC [•]) _{elim, base}	1.712	1.712	1.275	2.188	2.167	1.574
DFT/BHHLYP results obtained in ethanol solvent medium						
(IM [•]) _{elim, base}	0.000	0.000	0.000	0.000	0.000	0.000
(TS [•]) _{elim, base}	9.025	9.030	9.026	9.169	9.148	9.229
(PC [•]) _{elim, base}	8.777	9.168	8.444	8.703	9.111	8.281

^a The abbreviation TS[•] stands for transition state, IM[•] stands for the intermediate species and PC[•] denotes the product complex. The subscript "elim, base" represents reaction species obtained through the A-E mechanism performed in the presence of a base catalyst.

The rate constant for the dehydration step ($k_{\text{elim,base}}^{\tau}$) performed in basic medium is reported in Table 4.20; it has a value of $9.172 \times 10^3 \text{ s}^{-1}$ and $1.011 \times 10^6 \text{ s}^{-1}$ in benzene solvent medium and in ethanol solvent medium, respectively. These results suggest that THAP + $\bullet\text{OH}$ reaction is more kinetically favoured in a polar medium than in medium with less polar character. The $k_{\text{elim,base}}^{\tau}$ value is lower than k_{add}^{τ} , implying that the dehydration step is significantly slower than the $\bullet\text{OH}$ addition step, a result that is in agreement with the ΔE_{act} values reported earlier. A comparison of $k_{\text{elim,base}}^{\tau}$ and k_{elim}^{τ} indicates that the A-E mechanism is faster when the reaction is performed in basic medium than when it is performed without inclusion of the base.

4.4.3 Oxidation reaction performed with and without inclusion of O_2

The acylated tetrahydroxycyclohexadienyl radical (obtained in section 4.4.1) may undergo oxidation to yield a high order polyphenol derivative. The oxidation of acylated tetrahydroxycyclohexadienyl radical may be achieved without and with the inclusion of O_2 to form 2, 3, 4, 6-tetrahydroxyacetophenone as a major product. In this section, the results of the investigation on the reaction of acylated tetrahydroxycyclohexadienyl radical with and without inclusion of O_2 are presented and analysed.

4.4.3.1 Oxidation mechanism without inclusion of O_2

The oxidation of acylated tetrahydroxycyclohexadienyl radical ($(\text{IM}^{\tau})_{\text{add}}$) in the absence of O_2 was modelled by performing the C3–H3 bond scan, thereby eliminating the H radical from the ring, forming 2, 3, 4, 6-tetrahydroxyacetophenone. The scan is shown in Figure 4.33; it shows the existence of three stationary points; two minima and one maximum. All the three stationary points were optimised separately followed by frequency calculations on the optimised structures. The structure at the minimum corresponding to the C3–H3 bond distance of 1.102 Å and the one corresponding to the C3–H3 bond distance of 2.402 Å were found to have zero imaginary frequencies. The structure at the maximum was found to possess one imaginary frequency of magnitude (cm^{-1}) 769, 892 and 875 *in vacuo*, in benzene and in ethanol; it is therefore a transition state structure. The product complex found at the C3–H3 bond distance of 2.402 Å is denoted as $(\text{PC})_{\text{oxi}}$, while the transition state is denoted as $(\text{TS}^{\tau})_{\text{oxi}}$.

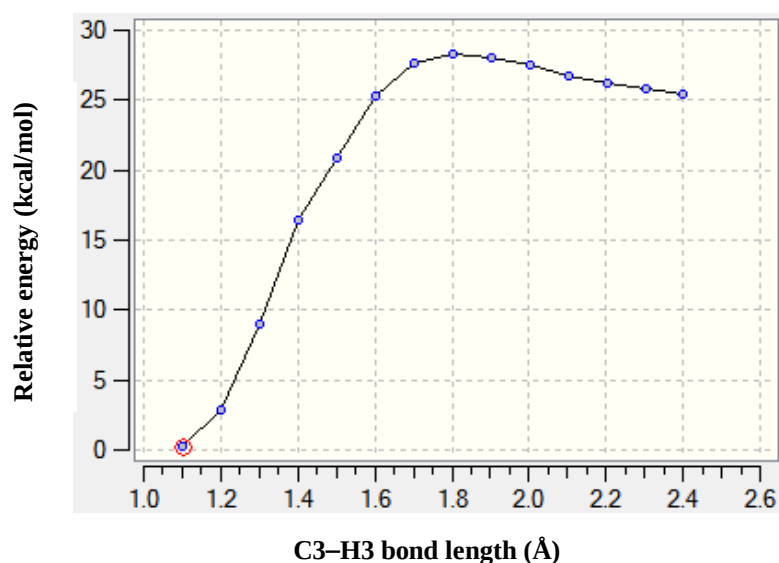


Figure 4.33: M06-2X/6-31+G(d, p) scan for the C3-H3 bond scan (in steps of 0.1 Å) for the THAP + $\bullet$ OH oxidation reaction without inclusion of O₂ in the reaction.

The geometries for $(TS^\ddagger)_{\text{oxi}}$ and $(PC)_{\text{oxi}}$, along with their corresponding molecular graphs, are shown in Figure 4.34. The electronic parameters at BCP are reported in Table 4.18; C3-H3 bond is longer in $(TS^\ddagger)_{\text{oxi}}$ in comparison to the value it has in $(IM^\ddagger)_{\text{add.}}$, which is evidenced by the decrease in the ρ value for the bond from $(IM^\ddagger)_{\text{oxi}}$ to $(TS^\ddagger)_{\text{oxi}}$. The C3-H3 bond in $(TS^\ddagger)_{\text{oxi}}$ is also characterised by $\nabla^2\rho$ that is greater than zero and a H value that is less than zero, implying that the C3-H3 bond; the $|V|/G$ ratio for the C3-H3 bond lies between the values 1 and 2, with inclination towards 2. All these parameters suggest that the bond is largely intermediate in strength with tendency towards a strong bond.

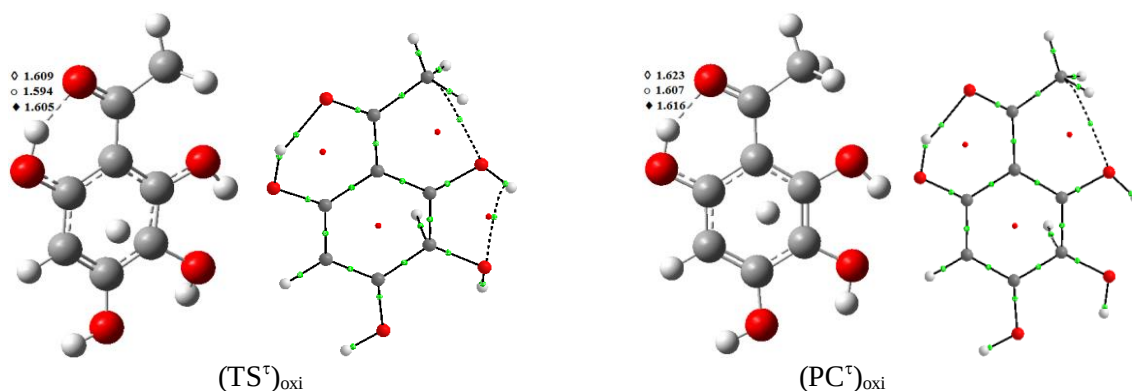


Figure 4.34: M06-2X/6-311++G(3df,2p) geometry for the transition state (on the left) and product complex (on the right) with their corresponding molecular graphs obtained from the oxidation reaction without inclusion of O₂. The bond lengths in the reaction species are obtained *in vacuo* (◊), in benzene (○) and in ethanol (◆) media. The first (PC[‡])_{elim,base} on the left is obtained in benzene while the second (PC[‡])_{elim,base} on the right is obtained in ethanol. The green dot within a given bond represents the bond critical point while the red dot within a given ring stands for the ring critical point.

(PC)_{oxi} is a complex between 2, 3, 4, 6-tetrahydroxyacetophenone and •H. The C3...H3 bond distance and the corresponding BCP data (e.g., $\nabla^2\rho$ and H) clearly indicate that there is minimal interactions between C3 and H3. 2, 3, 4, 6-tetrahydroxyacetophenone is characterised by the presence of two intramolecular hydrogen bonds, which are discernible in the molecular graph.

The relative energy values for the reaction species are reported in Table 4.19, while the energy profile for THAP + •OH is shown in Figure 4.35. ΔE_{act} (kcal/mol) has a value of 23.098 *in vacuo*, 23.819 in benzene and 25.282 in ethanol media, indicating that the •H removal is likely to occur faster *in vacuo* than in the presence of the solvent. A comparison of ΔE_{act} values corresponding to the •H removal step and the •OH addition step in the overall oxidation suggests that the •H removal step is the rate-limiting step.

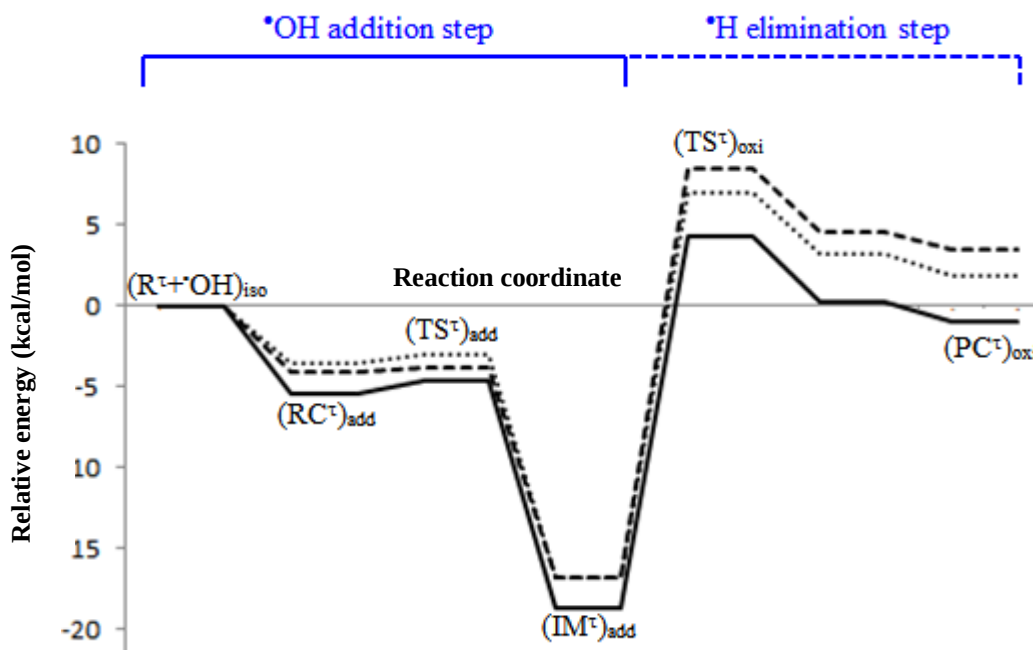


Figure 4.35: M06–2X/6-311++G(3df, 2p) energy profile (potential energy versus reaction coordinate) for the THAP + •OH reaction through the oxidation mechanism performed without inclusion of O₂. Results *in vacuo* (—), in benzene (.....) and in ethanol (-----) media.

The rate constant for the •H removal step of the oxidation mechanism is denoted as k^{τ}_{oxi} ; it has a range of the order of magnitude (s^{-1}) 10^{-5} – 10^{-8} , which is consistent with the experimental rate constant (that is to the order of 10^{-8} s^{-1}) for the •H removal from tetrahydroxycyclohexadienyl radical for the phloroglucinol + •OH reaction [274]. The k^{τ}_{oxi} value is significantly lower than the k^{τ}_{add} value, implying that the •H elimination step is slower than the •OH addition step. A comparison of the k^{τ}_{oxi} value across the different media, suggests that THAP + •OH is likely preferred in gaseous phase than in the presence of the solvent. These results obtained are in agreement with the analysis of ΔE_{act} obtained for THAP + •OH in different media.

4.4.3.2 Oxidation mechanism performed with inclusion of O₂

The oxidation of acylated tetrahydroxycyclohexadienyl radical (IM[•])_{oxi} in the presence of O₂ was considered to proceed through three main steps; the addition of O₂ to (IM[•])_{oxi}, forming acylated tetrahydroxycyclohexadienylperoxyl radical, the elimination of •OOH from the formed acylated tetrahydroxycyclohexadienylperoxyl radical (giving rise to acylated trihydroxycyclohexadienone anion radical) and the tautomerisation of acylated trihydroxycyclohexadienone anion radical to yield 2, 3, 4, 6-tetrahydroxyacetophenone. In respect to Figure 1.1, the numbering of the oxygen atoms on O₂, when interacting with THAP are given the numbers O14 and O15. The THAP + •OH reaction through the oxidation mechanism was studied *in vacuo* and in non-polar media.

The O₂ addition step was achieved by first optimising a complex structure involving the interaction of (IM[•])_{oxi} (obtained in section 4.4.1) and O₂. The product of the interaction is the acylated tetrahydroxycyclohexadienylperoxyl radical complex; it is denoted as (IM[•])_{oxi,O2}. (IM[•])_{oxi,O2} geometry is shown in Figure 4.36 and its corresponding molecular graph is shown in Figure 4.37; it is characterised by the existence of the C2...O14 intermolecular bond, which has a distance of 2.827 Å *in vacuo* and 3.291 Å in benzene. The molecular graph also shows the existence of the two six member rings and two five member rings, which are confirmed by the existence of ring critical points; furthermore, a cage critical point is present in a region between the five member ring and the six member ring, which also contributes to the stability of (IM[•])_{oxi,O2}. The electronic properties at BCPs for (IM[•])_{oxi,O2} are reported in Table 4.23, the |V|/G value is < 1 for the C2...O14 bond, implying that it is a closed shell type of an interaction.

The C2...O14 bond in (IM[•])_{oxi,O2} was then scanned with the objective of forming a covalent bond between O14 to C2; the outcome of the C2...O14 bond scan is shown in Figure 4.38; the graph is characterised by the existence of two minima points, located at the C2...O14 bond distance of 3.291 Å and 1.491 Å, as well as one maximum point, which is located at the C2...O14 bond distance of 2.191 Å. Frequency calculations were performed on the optimised structures at each minimum points and maximum point. The individual structures at each minimum point gave zero imaginary frequencies while the

structure at the maximum point gave one imaginary frequency of magnitude (cm^{-1}) 210 *in vacuo* and 138 in benzene. The structure found at the minimum point corresponding to the C2...O14 bond distance of 3.291 Å is $(\text{IM}^\tau)_{\text{oxi},\text{O}_2}$, while the structure found at the minimum point corresponding to the C2...O14 bond distance of 1.491 Å is given the $(\text{IM}^\tau-1)_{\text{oxi},\text{O}_2}$ symbol. The structure at the maximum point corresponds to the transition state; it is designated with the $(\text{TS}^\tau-1)_{\text{oxi},\text{O}_2}$ symbol. The geometries and the molecular graphs of $(\text{TS}^\tau-1)_{\text{oxi},\text{O}_2}$ and $(\text{IM}^\tau-1)_{\text{oxi},\text{O}_2}$ are also shown in Figure 4.36 and Figure 4.37, respectively, while the electronic properties at BCPs are reported in Table 4.23.

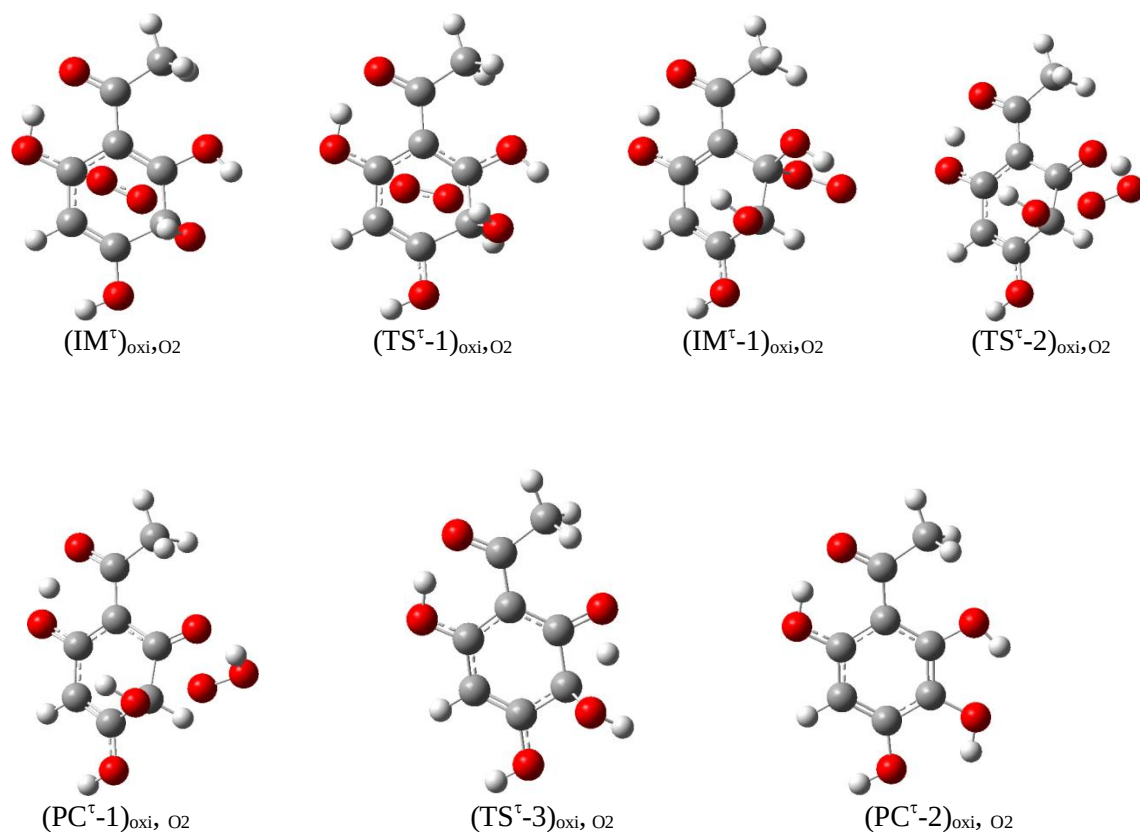


Figure 4.36: M06–2X/6-311++G(3df, 2p) THAP + $\bullet\text{OH}$ reaction species for the oxidation reaction performed with the inclusion of the O_2 molecule.

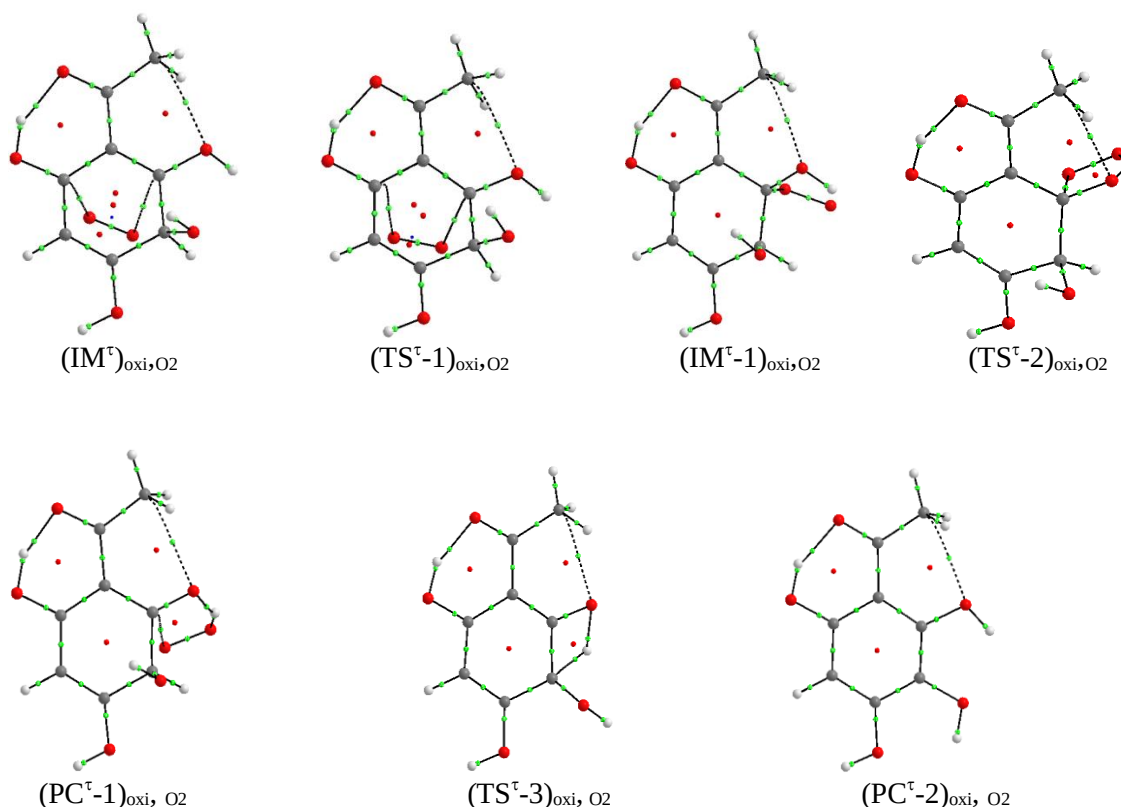


Figure 4.37: M06-2X/6-311++G(3df, 2p) molecular graphs for the THAP + •OH oxidation reaction species obtained when the reaction was performed with the inclusion of O₂. The green dot within a given bond represents the bond critical point while the red dot within a given ring stands for the ring critical point.

Table 4.23: M06-2X/6-311++G(3df, 2p) bond critical point properties for selected bonds within the THAP + •OH oxidation reaction species obtained when the reaction was performed with the inclusion of O₂.

structure ^a and bond type	electron density ρ ($e\text{\AA}^3$)	laplacian of the electron density $\nabla\rho^2$ ($e\text{\AA}^5$)	potential electron energy density V (Hartree)	kinetic electron energy density G (Hartree)	total electron energy density H (Hartree)
(IM) _{add,O2}					
O12...H9	0.055167	0.151191	-0.056810	0.047304	-0.009510
C12...O7	0.014892	0.067275	-0.012111	0.014465	0.002354
C2...O14	0.013934	0.042894	-0.008743	0.009733	0.000990
C6...O15	0.015286	0.048755	-0.009828	0.011008	0.001180
(TS-1) _{add,O2}					
O12...H9	0.065448	0.149231	-0.069210	0.053259	-0.015950
C12...O7	0.014364	0.064732	-0.011571	0.013877	0.002306
C2...O14	0.043135	0.098474	-0.030345	0.027482	-0.002860
C6...O15	0.018959	0.059934	-0.012307	0.013645	0.001338
(IM-1) _{add,O2}					
O12...H9	0.080483	0.138384	-0.089030	0.061813	-0.027220
C12...O7	0.013516	0.059426	-0.010731	0.012794	0.002063

C2–O14	0.224487	–0.447534	–0.374796	0.131456	–0.243340
O7–H7	0.365201	–2.755934	–0.827771	0.069394	–0.758380
(TS-2) _{add,O2}					
O12…H9	0.085379	0.132155	–0.095871	0.064455	–0.031420
C12…O7	0.014212	0.058979	–0.011174	0.012959	0.001785
C2…O14	0.077492	0.114833	–0.065391	0.047049	–0.018340
O7–H7	0.203286	–0.636522	–0.347213	0.094041	–0.253170
O15–H7	0.151975	–0.141480	–0.204842	0.084736	–0.120110
(PC-1) _{add,O2}					
O12…H9	0.085770	0.130308	–0.096251	0.064414	–0.031840
C12…O7	0.013599	0.056418	–0.010704	0.012404	0.001700
C2…O14	0.015072	0.055380	–0.011464	0.012654	0.001190
O7…H7	0.040952	0.128705	–0.038521	0.035349	–0.003170
O15–H7	0.339775	–2.568344	–0.761794	0.059854	–0.701940
(TS-3) _{add,O2}					
C12…O7	0.066925	0.142110	–0.070202	0.052865	–0.017340
C2…O14	0.011257	0.045778	–0.008426	0.009935	0.001509
C3…H3	0.117437	–0.087423	–0.116186	0.047165	–0.069020
O7…H3	0.143870	–0.093229	–0.188458	0.082576	–0.105880
(PC-2) _{add,O2}					
C12…O7	0.057258	0.153133	–0.059563	0.048923	–0.010640
C2…O14	0.014847	0.067444	–0.012130	0.014496	0.002366
O7–H3	0.364535	–2.782094	–0.829699	0.067088	–0.762610

^a The abbreviation IM stands for the intermediate species, TS stands for the transition state and PC denotes the product complex.

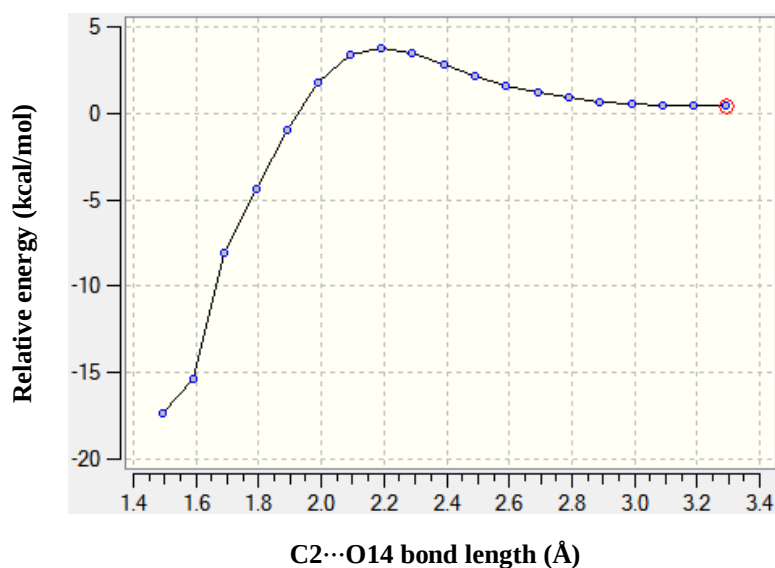


Figure 4.38: BHHLYP/6-31+G(d, p) scan (in steps of 0.1 Å) for the C2...O14 bond for the addition of O₂ to the acylated tetrahydroxycyclohexadienyl radical species.

The C2...O14 bond in (TS[‡]-1)_{oxi,O2} has a distance (Å) of 2.271 *in vacuo* and 2.368 in benzene. A comparison of the C2...O14 bond in (TS[‡]-1)_{oxi,O2} and in (IM[‡])_{oxi,O2} suggests that it significantly shortens on going from (IM[‡])_{oxi,O2} to (TS[‡]-1)_{oxi,O2}. The molecular graph also shows the existence of the O12...H9 bond (which forms part of the six member ring), the C12...O7 bond (which forms part of the five member ring) and the C6...O15 bond (which forms part of the five member ring); moreover a cage critical point, involving C6-C1-C2-O14-O15 and C1-C2-C3-C4-C5-C6 rings, is also present in the geometry for (TS[‡]-1)_{oxi,O2}. The value of the electron density for the C2...O14 bond increases from (IM[‡])_{oxi,O2} to (TS[‡]-1)_{oxi,O2}, indicating that the C2...O14 bond is stronger in the geometry for (TS[‡]-1)_{oxi,O2} than in the geometry for (IM[‡])_{oxi,O2}. $\nabla^2\rho > 0$ while $H < 0$ for the C2...O14 bond in (TS[‡]-1)_{oxi,O2}, implying that it can be classified as an intermediary between the weak and the strong interactions; the fact that the C2...O14 bond is intermediary between a strong and a weak interaction is confirmed by its $|V|/G$ ratio, which is 1.1.

(IM[‡]-1)_{oxi,O2} has a C2–O14 covalent bond of magnitude 1.502 Å *in vacuo* and 1.507 Å in benzene as well as the C1–C6–O14–O15 torsion angle of 168° in all the media. The molecular graph shows the presence of three rings. The ρ value for the C2–O14 bond in (IM[‡]-1)_{oxi,O2} is significantly higher than the C2...O14 bond in (TS[‡]-1)_{oxi,O2}, indicating that the C2–O14 bond is a stronger bond in (IM[‡]-1)_{oxi,O2} compared to C2...O14 bond in (TS[‡]-1)_{oxi,O2}, which is also confirmed by the negative values of $\nabla^2\rho$, and H as well as the $|V|/G$ ratio of 2.9.

The energetic properties for the geometries involved in the O₂ addition step are reported in Table 4.24. The ΔE_{act} (kcal/mol) is 0.853 and 0.159 *in vacuo* and in benzene, respectively. A comparison of the ΔE_{act} values for the O₂ addition step and the •H removal step (in the oxidation mechanism performed without inclusion of O₂) suggests that the O₂ addition step has a lower ΔE_{act} value than the •H elimination step, indicating that the oxidation mechanism is better performed with than without inclusion of O₂.

Table 4.24: Relative electronic energy (ΔE , kcal/mol), enthalpy (ΔH , kcal/mol) and Gibbs free energy (ΔG , kcal/mol) for the THAP + $\bullet OH$ oxidation reaction species obtained when the oxidation reaction was performed in the presence of O_2 .

structure ^a	results in different media obtained with the 6-31++G(d,p) basis set			results in different media obtained with the 6-311++G(3df,2p) basis set		
	relative electronic energy (ΔE , kcal/mol)	Relative enthalpy (ΔH , kcal/mol)	relative Gibbs free energy (ΔG , kcal/mol)	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative Gibbs free energy (ΔG , kcal/mol)
DFT/M06-2X results obtained <i>in vacuo</i>						
(IM ⁺) _{oxi,O2}	0.000	0.000	0.000	0.000	0.000	0.000
(TS ⁻¹) _{oxi,O2}	0.853	0.152	2.058	1.3303	0.616	2.597
(IM ⁻¹) _{oxi,O2}	-17.379	-18.367	-15.688	-15.922	-16.869	-14.209
(TS ⁻²) _{oxi,O2}	-9.397	-10.575	-7.749	-8.210	-9.419	-6.505
(PC ⁻¹) _{oxi,O2}	-16.333	-16.547	-16.501	-16.246	-16.503	-16.266
(TS ⁻³) _{oxi,O2}	50.213	50.115	40.259	50.434	50.351	40.540
(PC ⁻²) _{oxi,O2}	-23.604	-23.508	-33.567	-23.793	-23.791	-33.606
DFT/M06-2X results obtained in benzene solvent medium						
(IM ⁺) _{oxi,O2}	0.000	0.000	0.000	— ^b	— ^b	— ^b
(TS ⁻¹) _{oxi,O2}	0.159	-0.515	1.536			
(IM ⁻¹) _{oxi,O2}	-17.570	-18.536	-15.643			
(TS ⁻²) _{oxi,O2}	-9.855	-11.029	-7.976			
(PC ⁻¹) _{oxi,O2}	-17.291	-17.514	-17.350			
(TS ⁻³) _{oxi,O2}	47.419	44.918	37.663			
(PC ⁻²) _{oxi,O2}	-25.393	-27.645	-35.243			
DFT/MPW1K results obtained <i>in vacuo</i>						
(IM ⁺) _{oxi,O2}	0.000	0.000	0.000	0.000	0.000	0.000
(TS ⁻¹) _{oxi,O2}	2.298	1.137	5.749	7.375	8.639	-0.341
(IM ⁻¹) _{oxi,O2}	-15.208	-16.663	-11.253	-9.640	-8.623	-16.931
(TS ⁻²) _{oxi,O2}	-6.967	-8.614	-3.044	-1.772	-0.980	-9.060
(PC ⁻¹) _{oxi,O2}	-21.025	-21.690	-19.887	-16.208	-14.465	-16.887
(TS ⁻³) _{oxi,O2}	48.672	48.112	40.922	37.585	39.395	18.803
(PC ⁻²) _{oxi,O2}	-25.489	-25.918	-33.122	-35.623	-33.465	-54.908
DFT/MPW1K results obtained in benzene solvent medium						
(IM ⁺) _{oxi,O2}	0.000	0.000	0.000	0.000	0.000	0.000
(TS ⁻¹) _{oxi,O2}	— ^c	— ^c	— ^c	— ^c	— ^c	— ^c
(IM ⁻¹) _{oxi,O2}	-14.997	-16.551	-10.100	-13.973	-14.933	-10.378
(TS ⁻²) _{oxi,O2}	-7.2107	-8.9527	-2.4372	-6.5129	-7.6901	-3.0233
(PC ⁻¹) _{oxi,O2}	-22.208	-22.928	-20.454	-12.219	-12.336	-20.415
(TS ⁻³) _{oxi,O2}	56.158	55.494	49.311	46.237	46.100	38.247
(PC ⁻²) _{oxi,O2}	-26.992	-27.484	-33.839	-27.041	-27.027	-35.089
DFT/BHLLYP results obtained <i>in vacuo</i>						
(IM ⁺) _{oxi,O2}	0.000	0.000	0.000	0.000	0.000	0.000
(TS ⁻¹) _{oxi,O2}	4.125	2.937	7.779	4.671	3.486	8.410
(IM ⁻¹) _{oxi,O2}	-13.117	-14.605	-8.892	-12.005	-13.453	-7.742
(TS ⁻²) _{oxi,O2}	-3.477	-5.166	0.686	-2.701	-4.366	1.480
(PC ⁻¹) _{oxi,O2}	-15.828	-17.201	-12.002	-10.447	-11.020	-18.330
(TS ⁻³) _{oxi,O2}	50.833	50.206	43.378	50.925	50.300	43.617
(PC ⁻²) _{oxi,O2}	-26.119	-26.618	-33.469	-26.442	-26.985	-33.658
DFT/BHLLYP results obtained in benzene solvent medium						
(IM ⁺) _{oxi,O2}	0.000	0.000	0.000	0.000	0.000	0.000
(TS ⁻¹) _{oxi,O2}	3.465	2.228	7.671	4.051	2.8075	8.259
(IM ⁻¹) _{oxi,O2}	-13.028	-14.587	-8.135	-11.839	-13.354	12.180
(TS ⁻²) _{oxi,O2}	-3.981	-5.735	0.771	-3.981	-5.735	0.771
(PC ⁻¹) _{oxi,O2}	-13.747	-14.440	-20.842	-13.828	-14.493	-21.027
(TS ⁻³) _{oxi,O2}	48.300	47.571	41.502	48.506	47.797	41.692
(PC ⁻²) _{oxi,O2}	-27.602	-28.119	-34.509	-27.838	-28.403	-34.731

^a The acronym RC represents reactant complex, TS represents transition state, IM represents intermediate, PC represents product complex and P_{iso} stands for isolated product. The abbreviation “oxi” represents reaction species obtained through oxidation mechanism

^b On optimization, the geometry obtained did not corresponding to the desired intermediate structure, as such the rest of the calculations were not meaningful to calculate.

^c On optimization the transition state structure could not be obtained.

The rate constant (k^{τ}_{1,O_2}) for the O_2 addition step is reported in Table 4.20; it is $1.825 \times 10^{11} \text{ s}^{-1}$ *in vacuo* and $1.125 \times 10^{10} \text{ s}^{-1}$ in benzene. A comparison of k^{τ}_{1,O_2} value and k^{τ}_{oxi} value suggests that k^{τ}_{1,O_2} has a higher value than k^{τ}_{oxi} , so that it is possible to deduce that the oxidation mechanism is kinetically preferred when performed with the inclusion of O_2 than without inclusion of O_2 . The analysis for kinetic parameters is consistent with the analysis for activation energetic parameter.

The elimination of $\bullet OOH$ from $(IM^{\tau}-1)_{oxi,O_2}$ was initiated by performing the $O15 \cdots H7$ bond scan starting from $(IM^{\tau}-1)_{oxi,O_2}$. The outcome of the $O15 \cdots H7$ bond scan is shown in Figure 4.39; it shows the presence of a minimum point at the $O15 \cdots H7$ bond distance of 2.223 Å, a maximum point located at the $O15 \cdots H7$ bond distance of 1.223 Å and another minimum point located at the $O15 \cdots H7$ bond distance of 1.023 Å. The outcome of frequency calculations upon the optimised structures found at each minimum point gave zero imaginary frequencies while the structure found at the maximum possesses one imaginary frequency of magnitude (cm^{-1}) 737 *in vacuo* and 648 in benzene; it corresponds to the simultaneous stretching vibrations for the $C2 \cdots O14$ bond and the $O15 \cdots H7$ bond. The minimum point located at the $O15 \cdots H7$ bond distance of 2.223 Å is $(IM^{\tau}-1)_{oxi,O_2}$ while the minimum point located at the $O15 \cdots H7$ bond distance of 1.023 Å corresponds to the acylated trihydroxycyclohexadienone anion radical and $\bullet OOH$ complex; it is denoted throughout the study as $(PC^{\tau}-1)_{oxi,O_2}$. The structure at the maximum point located at the $O15 \cdots H7$ bond distance is a transition state; it is represented as $(TS^{\tau}-2)_{oxi,O_2}$. Geometries of $(TS^{\tau}-2)_{oxi,O_2}$ and $(PC^{\tau}-1)_{oxi,O_2}$ are shown in Figure 4.36 while their corresponding molecular graphs are shown in Figure 4.37. The electronic properties at BCPs for $(TS^{\tau}-2)_{oxi,O_2}$ and $(PC^{\tau}-1)_{oxi,O_2}$ are reported in Table 4.23; their relative energies are reported in Table 48.

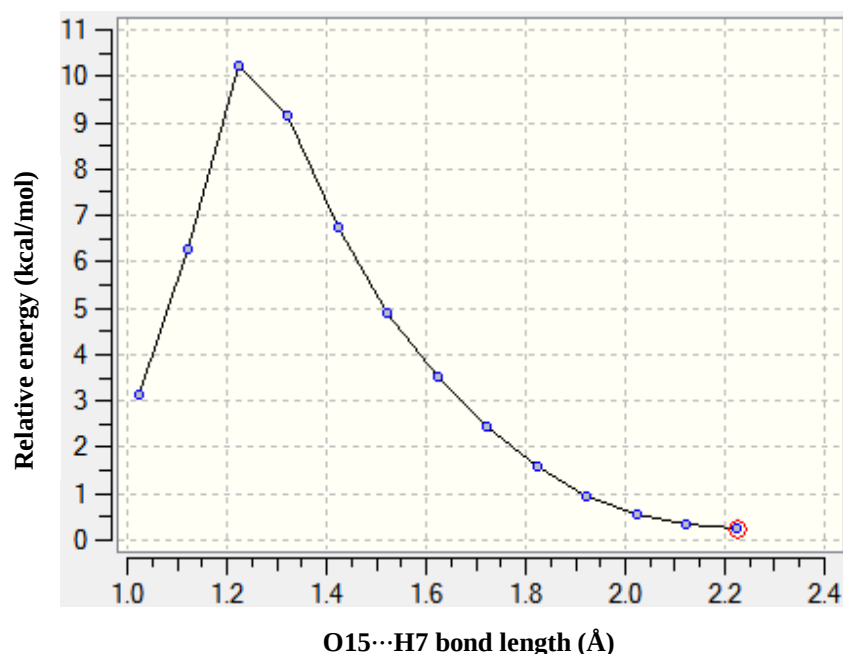


Figure 4.39: M06–2X/6-31+G(d, p) scan (in steps of 0.1 Å) for the O15...H7 bond for the elimination of •OOH from acylated tetrahydroxycyclohexadienylperoxyl radical.

(TS^τ-2)_{oxi,O2} has three intermolecular bonds, which are, the C2...O14 bond (with a distance of 1.985 Å *in vacuo* and 2.002 Å in benzene), the O7...H7 bond (with a distance of 1.145 Å *in vacuo* and 1.131 Å in benzene) and the O15...H7 bond (with a distance of 1.269 Å *in vacuo* and 1.287 Å in benzene). The C2...O14 and O7...H7 bonds elongate while the O15...H7 bond shortens in the geometry for (TS^τ-2)_{oxi,O2} in comparison to the values they have in the geometry for (IM^τ-1)_{oxi,O2}, indicating that the C2...O14 bond and the O7...H7 bond incline towards breaking while the O15...H7 bond inclines towards forming a strong bond in (TS^τ-2)_{oxi,O2}. The molecular graph for (TS^τ-2)_{oxi,O2} confirms the presence of the C2...O14, O7...H7 and the O15...H7 bonds. The electron density is decreasing for the C2...O14 bond and the O7...H7 bond while it is increasing for the O15...H7 bond from (IM^τ-1)_{oxi,O2} to (TS^τ-2)_{oxi,O2}, indicating that the C2...O14 bond and O7...H7 bond are weaker while the O15...H7 bond is stronger in (TS^τ-2)_{oxi,O2} than in (IM^τ-1)_{oxi,O2}. The |V|/G ratio for the C2...O14 bond, O7...H7 bond and the O15...H7 bond in (TS^τ-2)_{oxi,O2} is 1.4, 3.7 and 2.4, respectively.

(PC^τ-1)_{oxi,O2} is characterised by the interaction of the acylated trihydroxycyclohexadienone anion radical and •OOH; the interaction formed is the O7...H7–O15 hydrogen bond, where •OOH is the hydrogen donor while acylated trihydroxycyclohexadienone anion radical is the hydrogen acceptor. The C2...O14 bond is approximately 2.7 Å in both media, which implies that it is longer in (PC^τ-1)_{oxi,O2} than in (TS^τ-2)_{oxi,O2}. A comparison of the ρ values for the O7...H7 and C2...O14 bonds in (PC^τ-1)_{oxi,O2} and (TS^τ-2)_{oxi,O2} suggests that they are weaker in (PC^τ-1)_{oxi,O2} than in (TS^τ-2)_{oxi,O2}.

The ΔE_{act} for the •OOH elimination step is 7.982 kcal/mol *in vacuo* and 7.715 kcal/mol in benzene. A comparison of the ΔE_{act} values for the •OOH elimination step and the O₂ addition step suggests that the •OOH elimination step is likely to occur slower than the O₂ addition step. The value of the rate constant for the •OOH elimination step ($k_{2,O2}^{\tau}$) is reported in Table 4.20. A comparison of the $k_{2,O2}^{\tau}$ value and the $k_{1,O2}^{\tau}$ value suggests that the •OOH elimination step is likely to occur slower than the O₂ addition step.

The possibility of the conversion of (PC^τ-1)_{oxi,O2}, which has a keto group, to the enol group was taken into consideration by performing the O7...H3 bond scan, which is shown in Figure 4.40; it shows the two minima points located at 2.642 Å and 0.942 Å and one maximum point located at 1.342 Å. The structure at the two minimum points were optimised separately and frequency calculations were performed at the same level of optimisation; the structures at the two minimum points gave zero imaginary frequencies while the structure at the maximum point gave one imaginary frequency (which has the magnitude (cm⁻¹) 2130 *in vacuo* and 2146 in benzene). The minimum point located at 2.642 Å corresponds to (PC^τ-1)_{oxi,O2}, the maximum point corresponds to the transition state ((TS^τ-3)_{oxi,O2}) and the other minimum point located at 0.942 Å corresponds to the product complex (2, 3, 4, 6-tetrahydroxyacetophenone and the •OOH). The 2, 3, 4, 6-tetrahydroxyacetophenone is denoted throughout the work as (PC^τ-2)_{oxi,O2}. The geometry and the corresponding molecular graph for (TS^τ-3)_{oxi,O2} and (PC^τ-2)_{oxi,O2} are shown in Figure 4.36 and Figure 4.37, respectively. The electronic properties at BCPs for (TS^τ-3)_{oxi,O2} and (PC^τ-2)_{oxi,O2} are reported in Table 4.23; their relative energies are

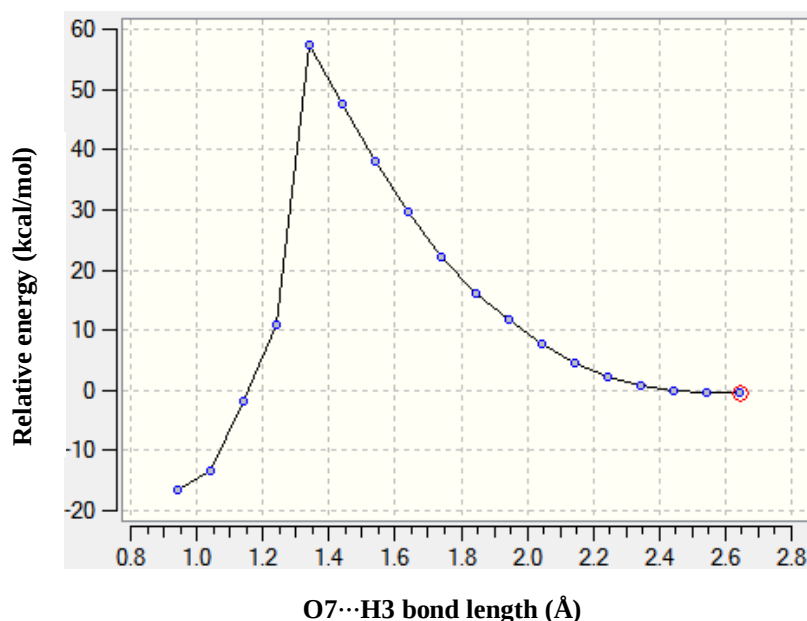


Figure 4.40: M06–2X/6-31+G(d, p) scan (in steps of 0.1 Å) for the O7...H3 bond for the isomerisation of acylated trihydroxycyclohexadienone anion radical to tetrahydroxyacetophenone.

reported in Table 4.24. $(TS^{\tau-3})_{\text{oxi},\text{O}_2}$ has the C3...H3 bond with a distance of 1.437 Å *in vacuo* and 1.582 Å in benzene as well as the O7...H3 bond with a distance of approximately 1.295 in both the media. The $\nabla^2\rho$ and H values for the C3...H3 bond and the O7...H3 bond are all negative and closer to zero; their $|V|/G$ values are 2.4 and 2.3, respectively, implying that the C3...H3 bond and the O7...H3 bond are strong interactions within $(TS^{\tau-3})_{\text{oxi},\text{O}_2}$. However, in comparison to their values in $(PC^{\tau-1})_{\text{oxi},\text{O}_2}$, an inference can be made that both the C3...H3 bond and the O7...H3 bond in $(TS^{\tau-3})_{\text{oxi},\text{O}_2}$ are weaker than in $(PC^{\tau-1})_{\text{oxi},\text{O}_2}$. $(PC^{\tau-2})_{\text{oxi},\text{O}_2}$ is identifiable by the presence of the O7–H3 bond; it has a length of approximately 0.965 Å. The $\nabla^2\rho$ and H values for the O7–H3 bond are all negative, indicating that it has the strong interaction characters, which is confirmed by the $|V|/G$ ratio, which is 12.8.

The energy profile for the overall oxidation mechanism is shown in Figure 4.41. The ΔE_{act} value for the isomerisation step is 66.546 kcal/mol *in vacuo* and 64.716 kcal/mol in benzene, indicating that it has a higher barrier compared to the O₂ addition step and the •OOH elimination step; in this way, the isomerisation step is a rate-limiting step for the

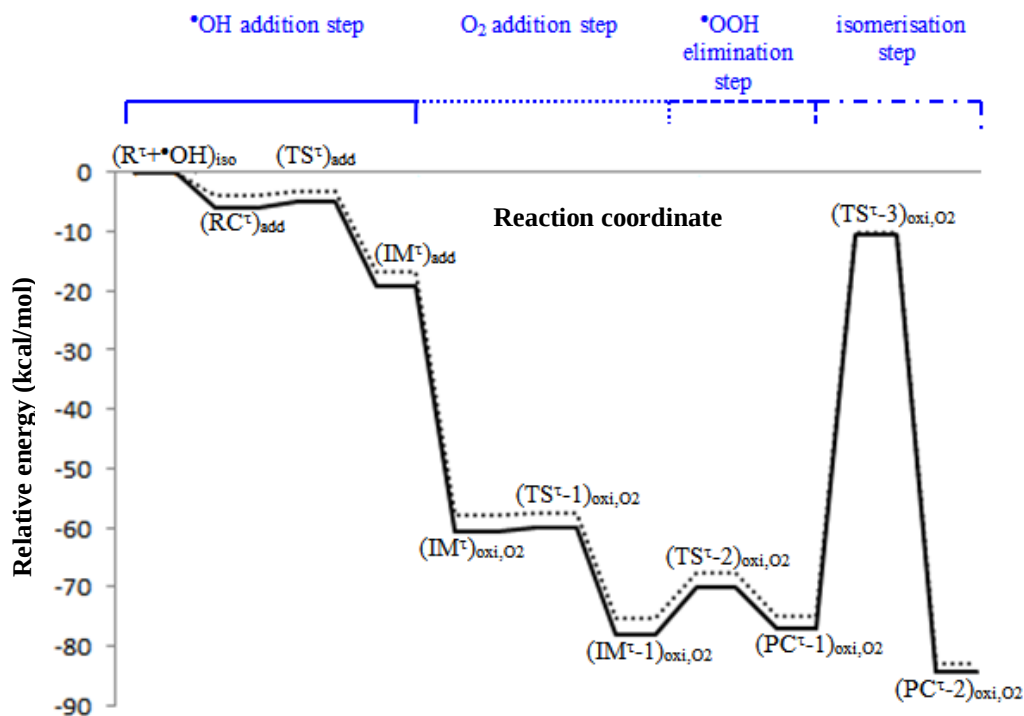


Figure 4.41: Energy profile (potential versus reaction coordinate) for the THAP + •OH oxidation reaction performed with inclusion of O₂. M06–2X/6-311++G(d, p) results *in vacuo* (—) and in benzene (.....) media.

overall oxidation reaction mechanism. The ΔG value, taken as a difference in Gibbs free energy value for $(PC^{\tau-2})_{oxi,O_2}$ and $(RC^{\tau})_{add}$, is negative, implying that the THAP + •OH reaction through oxidation performed with inclusion of O₂ is spontaneous. The isomerisation reaction rate constant is reported in Table 4.20; it is $1.453 \times 10^{-29} \text{ s}^{-1}$ *in vacuo* and $2.773 \times 10^{-28} \text{ s}^{-1}$ in benzene, indicating that isomerisation reaction is significantly slow compared to the O₂ addition step and the •OOH elimination step.

4.5 Comparison of the performance of the calculation methods

The difference among the methods in the estimation of the intramolecular bond distances (i.e., bond lengths between atoms) concerns the second decimal digit while the difference in the intermolecular bond distances (e.g., hydrogen bond distances) may at times concern the first decimal digit; in other words, the difference between any two methods for estimation of the intermolecular bond distances may be significantly noticeable. The variation in the bond lengths and torsion angles are also significantly noticeable when the measure angle concern intermolecular interaction.

The difference in the value of *BDE*, *IP*, *PA*, *PDE* and *ETE* for any of the selected methods, in a given media, remains below ~ 1 kcal/mol. This result suggests that there are negligible differences in the ability of the methods to estimate the various reaction enthalpies.

The barrier height is smallest when calculated with the DFT/M06–2X method and often largest when calculated with the DFT/BHLYP method. This is despite the fact that the BHLYP functional has higher HF-like exchange percentage than the MPW1K functional. In other words, the estimation of the barrier height is not only dependent on the contribution of the HF-like exchange but may also depend on other factors. For instance, it is known that the MPW1K functional is designed specifically to take into consideration features related to kinetics of reactions for the purpose of surpassing the BHLYP in terms of estimation of barrier heights [277].

The two basis set that were utilised in the study have a difference in the second or the third decimal digit when estimating the bond length for the reaction species. The difference in the corresponding bond angles and torsion angles calculated with the two basis sets are also below 4° . These results suggest that there is minimal basis set dependence in determining the geometric parameters for the reaction species.

The barrier heights are generally influenced by the quality of a basis set and inclusion of electron correlation [278], for instance, it has been shown that larger basis sets generally leads to smaller barrier height than smaller basis sets [279]. In the current study the

difference in the barrier heights between the two basis sets remain below 1 kcal/mol, indicating that there is negligible differences in the estimation of the barrier heights between the two basis sets for the studied compounds.

4.6 Summary of the chapter

The results for FG + $\bullet$ OH and for THAP + $\bullet$ OH have been presented in this chapter. The outcome of the analysis of the reaction enthalpies suggests that phloracetophenone is a better $\bullet$ OH scavenger than phloroglucinol; the preferred scavenging site is the *ortho* phenolic OH not engaged in intramolecular hydrogen bonding. The preferred antioxidant mechanism against the hydroxyl radical is the hydrogen atom transfer mechanism. The hydrogen atom transfer is however preferably occurring through addition-elimination pathway rather than direct abstraction pathway.

The addition mechanism may proceed to lead in the formation of the phenoxyl radical through the A-E mechanism or it may proceed through oxidation to form the polyphenol product. The formation of the phenoxyl radical through the A-E mechanism proceed when a catalyst species is added into the reaction, which in this study was modelled by using a base catalyst. The oxidation of the intermediate species, obtained after the addition of the hydroxyl radical to the ring, to form a polyphenol preferably take place in the presence of the oxygen molecule.

The media also plays a significant role in determining the direction of the reaction. For instance, the FG + $\bullet$ OH and the THAP + $\bullet$ OH reactions are kinetically more preferred in ethanol than in benzene while they are thermodynamically more preferred in benzene than in ethanol. A comparison across the structures suggests that FG + $\bullet$ OH prefers to form phenoxyl radical while THAP + $\bullet$ OH preferably results in the formation of the polyphenol. A comparison of the selected calculation methods suggests that DFT/BHHLYP method tends to overestimate the barrier height with respect to the DFT/M06-2X method.

CHAPTER 5

REACTIONS OF PHLOROGLUCINOL AND PHLOROACETOPHENONE WITH $\bullet\text{OOH}$

5.1 Introduction

This chapter presents and discusses results obtained for the reaction of phloroglucinol and phloroacetophenone with peroxy radical species. As with the previous chapter, the reaction enthalpies for the HAT, SET-PT and SPLET mechanisms are discussed first to give a clear indication on the preferred mechanism out of the three mechanisms. The determination of a better $\bullet\text{OOH}$ scavenger between FG and THAP as well as the preferred reaction site on THAP are also discussed in terms of reaction enthalpies.

The reactions involving the phenol derivatives with $\bullet\text{OOH}$ occur largely through the DHAA mechanism (section 1.2). For this reason, this chapter only presents and discusses the results for the FG + $\bullet\text{OOH}$, THAP1 + $\bullet\text{OOH}$ and THAP2 + $\bullet\text{OOH}$ reactions through the DHAA mechanism. The discussion includes the analysis of the geometric, electronic, energetic and kinetic properties obtained for all the reactions.

5.2 Reaction enthalpies related to the HAT, SET-PT and SPLET mechanisms

The reaction enthalpies for the HAT, SET-PT and SPLET mechanisms are reported in Table 5.1 for both compounds. The different reaction enthalpy values (i.e., *BDE*, *IP*, *PDE*, *PA* and *ETE*) are discussed separately in the following subsections.

Table 5.1: Reaction enthalpy values (kcal/mol) for FG + •OOH and THAP + •OOH; the results are obtained by using the 6-311++G(3df, 2p) basis set.

structure ^a	hydrogen atom transfer mechanism (HAT)	single electron transfer-proton transfer mechanism (SET-PT)		Sequential proton-loss electron-transfer mechanism (SPLET)	
	ΔH_{BDE}^b (kcal/mol)	ΔH_{IP}^b (kcal/mol)	ΔH_{PDE}^b (kcal/mol)	ΔH_{PA}^b (kcal/mol)	ΔH_{ETE}^b (kcal/mol)
DFT/M06–2X results obtained <i>in vacuo</i>					
FG	5.353	104.856	–99.502	–32.506	37.859
THAP1	3.150	170.103	–166.953	–48.337	51.487
THAP2	9.009	170.103	–161.093	–46.016	55.025
DFT/M06–2X results obtained in benzene solvent medium					
FG	4.341	107.827	–103.486	–23.428	27.769
THAP1	2.931	107.598	–104.667	–35.258	38.189
THAP2	8.595	107.598	–99.003	–33.554	42.149
DFT/ M06–2X results obtained in ethanol solvent medium					
FG	3.014	42.270	–39.256	–8.138	11.152
THAP1	2.183	43.864	–41.681	–14.315	16.498
THAP2	8.456	43.864	–35.408	–14.012	22.468
DFT/MPW1K results obtained <i>in vacuo</i>					
FG	4.814	105.657	–100.843	–32.369	37.183
THAP1	3.049	170.730	–167.680	–48.414	51.463
THAP2	10.049	170.730	–160.681	–46.047	56.096
DFT/MPW1K results obtained in benzene solvent medium					
FG	4.049	108.383	–104.335	–23.478	27.527
THAP1	2.963	108.264	–105.302	–35.400	38.363
THAP2	9.713	108.264	–98.5515	–33.669	43.383
DFT/MPW1K results obtained in ethanol medium					
FG	2.106	42.269	–40.163	–8.579	10.685
THAP1	2.247	44.153	–41.906	–14.388	16.635
THAP2	8.990	44.153	–35.163	–14.136	23.126
DFT/BHHLYP results obtained <i>in vacuo</i>					
FG	–6.574	102.069	–108.644	–40.181	33.606
THAP1	–7.925	168.820	–176.745	–55.904	47.978
THAP2	–1.529	168.820	–170.349	–53.733	52.204
DFT/BHHLYP results obtained in benzene solvent medium					
FG	2.445	105.277	–102.832	–21.322	23.767
THAP1	1.815	106.552	–104.737	–32.896	34.711
THAP2	7.936	106.552	–98.616	–31.379	39.315
DFT/BHHLYP results obtained in ethanol solvent medium					
FG	0.545	39.446	–38.901	–6.578	7.123
THAP1	0.590	41.171	–40.581	–12.522	13.112
THAP2	6.704	41.171	–34.467	–12.457	19.161

^aThe acronyms FG and THAP represent phloroglucinol and acylated phloroglucinol structures respectively; the numbers 1 and 2 on THAP represent the reaction site *para* phenolic OH and reaction site *ortho* phenolic OH, respectively.

^b The acronym H_{BDE} stands for bond dissociation enthalpy, H_{IP} stands for ionization potential, H_{PA} stands for proton affinity, H_{PDE} stands for proton dissociation enthalpy and H_{ETE} stands for electron transfer enthalpy.

5.2.1 Analysis of the *BDE* values for the HAT mechanism

The *BDE* values for FG + •OOH and for THAP + •OOH are greater than zero (except for the DFT/BHHLYP results obtained *in vacuo*), implying that FG + •OOH and THAP + •OOH are endothermic in nature. These results are in good agreement with the *BDE* values obtained for the reaction of fisetin with •OOH [280].

The *BDE* values follow the order THAP1 < FG < THAP2, suggesting that THAP has a better $\bullet\text{OOH}$ scavenging activity than FG. A comparison of the different reaction sites on THAP suggests that THAP1 has a significantly lower *BDE* value than THAP2, indicating that the free phenolic H is easily transferred (to $\bullet\text{OOH}$) from the *ortho* reaction site than from the *para* reaction site. In other words, THAP1 + $\bullet\text{OOH}$ is more thermodynamically favoured to THAP2 + $\bullet\text{OOH}$. The *BDE* values decrease with the increase in the dielectric constant of the media, implying that FG + $\bullet\text{OOH}$ and THAP + $\bullet\text{OOH}$ prefer occurring in polar medium than *in vacuo* and in non-polar medium [284].

5.2.2 Analysis of the *IP* and *PDE* values for the SET-PT mechanism

The *IP* values are all positive, implying that the SET step (which is the first stage of the complete SET-PT mechanism) is endothermic in nature. FG + $\bullet\text{OOH}$ has a significantly lower *IP* value than THAP + $\bullet\text{OOH}$ *in vacuo* and in polar medium, however, there is no significant difference in the *IP* values obtained in non-polar medium; the implication of the results is that the electron is likely to be transferred in FG + $\bullet\text{OOH}$ than in THAP + $\bullet\text{OOH}$ *in vacuo* and in polar media. There is minimal difference between the *IP* values obtained for the THAP1 + $\bullet\text{OOH}$ and THAP2 + $\bullet\text{OOH}$ in all the media, implying that SET step does not depend on the reaction site of THAP. Analysis of the *IP* values obtained for FG + $\bullet\text{OOH}$ and for THAP + $\bullet\text{OOH}$ suggests that SET step is likely to occur in polar medium than *in vacuo* and in non-polar medium.

A comparison of the *BDE* value for the HAT mechanism and the *IP* value for the SET step (which is the rate-limiting step for SET-PT) suggests that the scavenging of peroxy radical by the two antioxidant compounds is likely to proceed through the HAT mechanism rather than through the SET-PT mechanism. The gap between the *BDE* and *IP* values is significantly lower in polar medium than *in vacuo* and in non-polar medium, which suggests that as the solvent polarity increases, the single electron transfer mechanism might compete with the hydrogen atom transfer mechanism.

The second step (i.e., PT step) of the SET-PT mechanism can be described to take place between $\text{FG}^{\bullet+}$ or $\text{THAP}^{\bullet+}$ (obtained as products in the first step of the SET-PT

mechanism) with ^-OOH . The *PDE* values, controlling the proton transfer step, are all negative, implying that the proton transfer step is an energy releasing reaction; the *PDE* values are -99.502 kcal/mol, -166.953 kcal/mol and -161.093 kcal/mol for $\text{FG}^{\bullet+} + ^-\text{OOH}$, $\text{THAP1}^{\bullet+} + ^-\text{OOH}$ and $\text{THAP2}^{\bullet+} + ^-\text{OOH}$, respectively *in vacuo*. The implication of these results is that the proton transfer step is more favoured in $\text{THAP}^{\bullet+} + ^-\text{OOH}$ than in $\text{FG}^{\bullet+} + ^-\text{OOH}$. Moreover, the findings also indicate that the *PDE* value is lower for $\text{THAP1}^{\bullet+} + ^-\text{OOH}$ than for $\text{THAP2}^{\bullet+} + ^-\text{OOH}$, indicating that the proton transfer step is preferred at the *ortho* reaction site to *para* reaction site. *PDE* (kcal/mol) for $\text{FG}^{\bullet+} + ^-\text{OOH}$ is -99.502 *in vacuo*, -103.486 in benzene and -39.256 in ethanol, suggesting that the PT step is preferred in non-polar medium than *in vacuo* and in polar medium. However, the *PDE* values are lower *in vacuo* than in polar and non-polar medium for $\text{THAP1}^{\bullet+} + ^-\text{OOH}$ and $\text{THAP2}^{\bullet+} + ^-\text{OOH}$, which indicates that the PT step is favoured in the absence of the solvent for the $\text{THAP}^{\bullet+} + ^-\text{OOH}$ reactions.

An assessment of both *PDE* and *IP* values suggests that *PDE* values are significantly lower than *IP* values, indicating that the proton transfer step is preferred to the single electron transfer step in SET-PT. However, the proton transfer step is not considered as the rate-limiting step for the overall SET-PT mechanism.

5.2.3 Analysis of the *PA* and *ETE* values for the SPLET mechanism

The *PA* values are all negative for the reactions involving neutral FG and THAP species with ^-OOH , implying that the proton loss step is an exothermic process in nature. However, the proton loss step is not the rate-limiting step for the overall SPLET mechanism. The *PA* value is lower for $\text{FG} + ^-\text{OOH}$ than for $\text{THAP} + ^-\text{OOH}$, indicating that the proton loss step is more favoured in $\text{THAP} + ^-\text{OOH}$ than in $\text{FG} + ^-\text{OOH}$. $\text{THAP1} + ^-\text{OOH}$ has a lower *PA* value than $\text{THAP2} + ^-\text{OOH}$, suggesting that the proton is easily lost at the *ortho* reaction site than at the *para* reaction site of THAP.

Analysis of the *PA* values (obtained in different media) for all the reactions suggests that the *PA* values decrease with an increase in the dielectric constant of the media; this implies that the proton loss step is more preferred *in vacuo* than in polar and in non-polar

media. A comparison of the *PA* value and *PDE* value suggests that the proton transfer step is more favoured in the SEP-PT mechanism than in the SPLET mechanism.

The electron transfer step (second step in the SPLET mechanism) was initiated starting from the FG^- and THAP^- obtained as product species from the proton loss step. *ETE* (controlling the electron transfer step) values are all positive, implying that the reactions involving the FG^- and THAP^- with $\bullet\text{OOH}$ are endothermic in nature. The electron transfer step is considered as the rate-limiting step for the overall SPLET mechanism. *ETE* values are significantly lower for $\text{FG}^- + \bullet\text{OOH}$ than for $\text{THAP}^- + \bullet\text{OOH}$, indicating that electron transfer is more likely in $\text{FG}^- + \bullet\text{OOH}$ than in $\text{THAP}^- + \bullet\text{OOH}$. Assessment of the *ETE* values for $\text{THAP1}^- + \bullet\text{OOH}$ and for $\text{THAP2}^- + \bullet\text{OOH}$ suggests that $\text{THAP1}^- + \bullet\text{OOH}$ is likely to occur than $\text{THAP2}^- + \bullet\text{OOH}$.

Analysis of the *ETE* values obtained in different media for all the reactions suggests that *ETE* values decrease with an increase in dielectric constant of the media; an inference that can be made is that the electron transfer step is more favoured in polar medium than *in vacuo* and in non-polar medium. A comparison of the *ETE* value for the SPLET mechanism and the *IP* value for the SEP-PT mechanism suggest that the electron transfer step prefers occurring through the SPLET mechanism to the SET-PT mechanism. The *ETE* values are higher than the *BDE* values for the HAT mechanism, implying that there is the preference for the molecules to scavenge the peroxy radical species through the HAT mechanism as against the SPLET mechanism.

Overall, the results of the findings reported here suggests that the $\bullet\text{OOH}$ scavenging mechanism is largely through the hydrogen atom transfer mechanism rather than electron-transfer mechanisms. However, although the preferred mechanism for the scavenging of $\bullet\text{OOH}$ is the hydrogen atom transfer mechanism, the process is slightly endothermic.

5.3 Direct hydrogen atom abstraction mechanism

The DHAA mechanism for $\text{FG} + \bullet\text{OOH}$ and $\text{THAP} + \bullet\text{OOH}$ results in the formation of the stable phenoxyl radical and hydrogen peroxide. The atom numbering used for FG and THAP in this section is shown in Figure 1.1.

5.3.1 Geometric, energetic and kinetic properties for $\text{FG} + \bullet\text{OOH}$

$\text{FG} + \bullet\text{OOH}$ was achieved through the interaction of FG and $\bullet\text{OOH}$, which results in the formation of the reactant complex. The reactant complex is denoted as RC; its geometry and corresponding molecular graph are shown in Figure 5.1. The oxygen that is not bonded to the hydrogen in $\bullet\text{OOH}$ is labelled O10 while the oxygen that is bonded to the hydrogen in $\bullet\text{OOH}$ is labelled O11. RC has two intermolecular H-bonds, which are $\text{O7-H7}\cdots\text{O10}$ and $\text{C3-H3}\cdots\text{O11}$. The $\text{O7-H7}\cdots\text{O10}$ bond is shorter than the $\text{C3-H3}\cdots\text{O11}$ bond. The fact that the $\text{O7-H7}\cdots\text{O10}$ bond is shorter than the $\text{C3-H3}\cdots\text{O11}$ bond is related to the fact that in the two H-bonds, the hydrogen bond donor group is different; it is phenolic O-H group in the case of the $\text{O7-H7}\cdots\text{O10}$ bond and it is the C-H group in the case of the $\text{C3-H3}\cdots\text{O11}$ bond. Generally, O-H group has a greater H-bond donating tendency than C-H group mainly because of the high electronegativity nature of the O atom in comparison with that of the C atom [281, 282].

The molecular graph for RC shows the presence of the $\text{O10}\cdots\text{H7}$ bond and the $\text{O11}\cdots\text{H3}$ bond; which form part of the seven member ring. The electronic properties at BCPs for RC are reported in Table 5.2. The $|V|/G$ ratio value is 0.9 for the $\text{O10}\cdots\text{H7}$ bond and 0.8 for the $\text{O11}\cdots\text{H3}$ bond, indicating that the two bonds have weak interaction characters. The relative energy for RC is reported in Table 5.3. The energy of RC is significantly lower than the total energies of the separate reactant species, implying that RC is the preferred starting geometry for $\text{FG} + \bullet\text{OOH}$ [284].

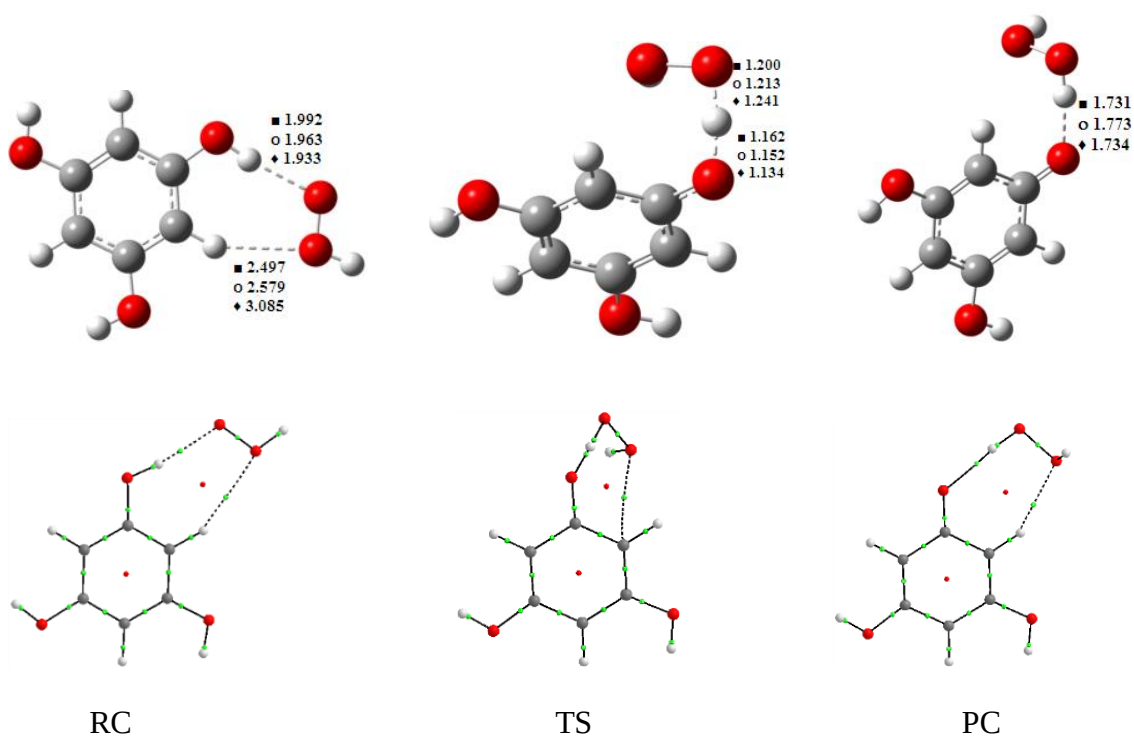


Figure 5.1: M06-2X/6-311++G(3df, 2p) geometries (first row) and the corresponding molecular graphs (second row) for the FG + •OOH reaction species. Some selected bond lengths (Å) that are shown on the geometries corresponds to results *in vacuo* (■), in benzene (o) and in ethanol (♦). The green dot within a given bond represents the bond critical point while the red dot within a given ring stands for the ring critical point. The abbreviation RC stands for reactant complex, TS stands for transition state and PC stands for product complex.

Table 5.2: Bond critical point properties for selected bonds within the FG^a + •OOH, THAP1^a + •OOH and THAP2^a + •OOH reaction species.

structure and bond type ^b	electron density ρ ($e\text{\AA}^{-3}$)	Laplacian of the electron density $\nabla^2\rho$ ($e\text{\AA}^{-5}$)	potential electron energy density V (Hartree)	kinetic electron energy density G (Hartree)	total electron energy density H (Hartree)
M06–2X/6-311++(3df, 2p) results obtained <i>in vacuo</i> for the FG + •OOH reaction					
RC					
C2–O7	0.309590	–0.536328	–0.856339	0.361129	–0.495210
O7–H7	0.378207	–2.974510	–0.882623	0.069498	–0.813130
O10...H7	0.020089	0.072403	–0.015082	0.016592	0.001510
O10–H3	0.005342	0.020181	–0.003479	0.004262	0.000783
TS					
C2–O7	0.299761	–1.162258	–0.369683	0.039559	–0.330120
O7...H7	0.293910	–1.111416	–0.365247	0.043697	–0.321550
O10...H7	0.294472	–1.115572	–0.365077	0.043092	–0.321990
C3...O11	0.207629	–0.652254	–0.361484	0.099210	–0.262270
PC					
C1–O7	0.400964	–0.426939	–1.345958	0.619612	–0.726350
O7...H7	0.031369	0.106742	–0.026561	0.026623	0.000064
O10–H7	0.371873	–2.947132	–0.868759	0.065988	–0.802770
O11... H7	0.010196	0.035413	–0.006587	0.007720	0.001133
M06–2X/6-311++(3df, 2p) results obtained <i>in vacuo</i> for the THAP1 + •OOH reaction					
RC					
C2–O7	0.300827	–0.489728	–0.798931	0.338249	–0.460680
O7–H7	0.359829	–2.740305	–0.819068	0.066996	–0.752070
O13...H7	0.023120	0.083821	–0.018474	0.019715	0.001241
O14–H3	0.007782	0.029741	–0.005315	0.006375	0.001060
TS					
C2–O7	0.324729	–0.958231	–0.468023	0.114233	–0.353790
O7–H7	0.324729	–0.958231	–0.468023	0.114233	–0.353790
O13...H7	0.063368	0.150858	–0.066772	0.052243	–0.014530
O13–O14	0.363288	–0.202318	–0.615197	0.282309	–0.332890
PC					
C2–O7	0.391562	–0.370228	–1.285317	0.596380	–0.688940
O7–H7	0.035948	0.119868	–0.032609	0.031288	–0.001320
O13...H7	0.352785	–2.679456	–0.801045	0.065591	–0.735450
O13–H3	0.009697	0.037141	–0.006641	0.007963	0.001322
M06–2X/6-311++(3df, 2p) results obtained <i>in vacuo</i> for the THAP2 + •OOH reaction					
RC					
C2–O7	0.304436	–0.486183	–0.817314	0.347884	–0.469430
O7–H7	0.359581	–2.737162	–0.817800	0.066755	–0.751050
O13...H8	0.023069	0.083900	–0.018348	0.019661	0.001313
O14– H5	0.007736	0.029022	–0.005165	0.006210	0.001045
TS					
C2–O7	0.340925	–0.505839	–0.988031	0.430785	–0.55725
O7...H7	0.174103	–0.287093	–0.261298	0.094762	–0.16654
O13...H8	0.191323	–0.478390	–0.305850	0.093126	–0.21272
PC					
C2–O7	0.390637	–0.355505	–1.284334	0.597729	–0.686610
O7–H7	0.033309	0.114275	–0.029717	0.029143	–0.000570
O13...H8	0.356112	–2.709538	–0.808656	0.065636	–0.743020
O13–H3	0.009611	0.037827	–0.007338	0.008398	0.001060
O14–H3	0.009870	0.042253	–0.007217	0.008890	0.001673

^aThe abbreviations FG denotes phloroglucinol and THAP denotes phloracetophenone. The numbers 1 and 2 on THAP indicates the *ortho* phenolic-OH and *para* phenolic-OH reaction site with respect to the acylated group, respectively.

^bThe abbreviation RC stands for reactant complex, TS stands for transition state and PC stands for product complex. C1, C2, O7, O10, H2, H7 indicates atoms and their positions, respectively.

Table 5.3: Relative electronic energy (ΔE , kcal/mol), enthalpy (ΔH , kcal/mol) and Gibbs free energy (ΔG , kcal/mol) for the FG + $\bullet\text{OOH}$ reaction species.

structure ^a	results obtained utilising the 6-31++G(d,p) basis set			results obtained utilising the 6-311++G(3df,2p) basis set		
	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative Gibbs free energy (ΔG , kcal/mol)	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative Gibbs free energy (ΔG , kcal/mol)
DFT/ M06-2X results obtained <i>in vacuo</i>						
(FG + $\bullet\text{OOH}$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-4.444	-4.657	4.969	-3.932	-4.071	5.040
(TS) _{abs}	8.318	7.817	18.301	9.331	8.881	18.974
(PC) _{abs}	-4.380	-4.637	5.038	-3.865	-4.062	5.317
(P + H ₂ O ₂) _{iso}	5.160	5.237	4.718	5.260	5.353	4.809
DFT/ M06-2X results obtained in benzene solvent medium						
(FG + $\bullet\text{OOH}$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-3.010	-2.702	5.191	-2.814	-2.414	4.523
(TS) _{abs}	9.967	9.513	19.780	10.788	10.319	20.607
(PC) _{abs}	-3.015	-2.704	5.164	-2.843	-2.560	5.465
(P + H ₂ O ₂) _{iso}	4.346	4.422	3.905	4.234	4.341	3.771
DFT/ M06-2X results obtained in ethanol solvent medium						
(FG + $\bullet\text{OOH}$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-1.973	-1.539	5.866	-1.648	-1.468	7.265
(TS) _{abs}	11.758	11.335	21.958	12.751	12.216	22.721
(PC) _{abs}	-2.045	-2.145	6.500	-1.515	-1.404	7.622
(P + H ₂ O ₂) _{iso}	2.159	2.428	1.527	2.490	2.634	1.975
DFT/MPW1K results obtained <i>in vacuo</i>						
(FG + $\bullet\text{OOH}$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-3.231	-2.918	4.800	-2.780	-2.428	4.918
(TS) _{abs}	12.124	11.653	22.120	13.478	13.035	23.373
(PC) _{abs}	-2.671	-2.455	-6.239	-1.451	-1.200	7.281
(P + H ₂ O ₂) _{iso}	4.223	4.330	3.758	4.678	4.814	4.187
DFT/MPW1K results obtained in benzene solvent medium						
(FG + $\bullet\text{OOH}$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-2.115	-2.354	7.020	-1.832	-2.011	7.152
(TS) _{abs}	13.673	13.246	23.522	14.991	14.571	24.790
(PC) _{abs}	-1.814	-1.608	7.172	-0.739	-0.515	8.241
(P + H ₂ O ₂) _{iso}	3.498	3.578	3.063	3.917	4.049	3.432
DFT/MPW1K results obtained in ethanol solvent medium						
(FG + $\bullet\text{OOH}$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-0.870	-0.555	7.390	-0.522	-0.243	7.002
(TS) _{abs}	15.649	15.234	25.675	16.820	16.348	26.716
(PC) _{abs}	-1.651	-1.266	6.522	-0.553	-0.297	7.880
(P + H ₂ O ₂) _{iso}	-11.251	1.544	0.698	1.915	2.106	1.371
DFT/BHLLYP results obtained <i>in vacuo</i>						
(FG + $\bullet\text{OOH}$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-4.224	-3.951	3.961	-2.974	-2.631	4.995
(TS) _{abs}	13.858	13.363	23.833	16.138	15.719	25.973
(PC) _{abs}	-5.331	-5.139	3.601	-3.245	-2.980	5.481
(P + H ₂ O ₂) _{iso}	1.844	1.922	1.413	-6.714	-6.574	-7.203
DFT/BHLLYP results obtained in benzene solvent medium						
(FG + $\bullet\text{OOH}$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-2.041	-1.827	6.651	-1.749	-1.486	6.560
(TS) _{abs}	16.045	15.641	25.796	17.518	17.105	27.002
(PC) _{abs}	-3.765	-3.555	5.210	-2.578	-2.361	6.355
(P + H ₂ O ₂) _{iso}	1.766	1.876	51.264	2.358	2.465	1.903
DFT/BHLLYP results obtained in ethanol solvent medium						
(FG + $\bullet\text{OOH}$) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
(RC) _{abs}	-0.712	-0.476	7.772	-0.707	-0.378	7.486
(TS) _{abs}	10.540	9.806	21.217	11.861	11.306	22.331
(PC) _{abs}	-3.248	-2.998	5.414	-2.651	-2.225	5.597
(P + H ₂ O ₂) _{iso}	-0.154	-0.574	-0.573	0.114	0.340	-0.465

^a The abbreviation RC denotes reaction complex, TS denotes transition states, PC denotes product complex and P_{iso} denotes isolated product species.

The scan of the O10...H7 bond in RC was performed with the aim of abstracting H7 from O7 in order to form a stable 4, 6-dihydroxyphenoxyl radical and hydrogen peroxide. The outcome of the scan is shown in Figure 5.2; it is characterised by the existence of two minimum points and one maximum point. The two minimum points are located at the O10...H7 bond distance of 2.014 Å and 1.015 Å while the maximum point is located at the O10...H7 bond distance of 1.215 Å. Optimisation and frequency calculations were performed on the individual structures found at each minimum point; each structure gave zero imaginary frequency, which implies that they are both minima on PES. The structure at the O10...H7 bond distance of 2.014 Å is actually RC while the structure at the O10...H7 bond distance of 1.015 Å corresponds to the product complex. The product complex is denoted as PC. The optimisation procedure was performed on the structure found at the maximum. The subsequent frequency calculations on the output structure indicate that the structure at the maximum point is the transition state, this is confirmed

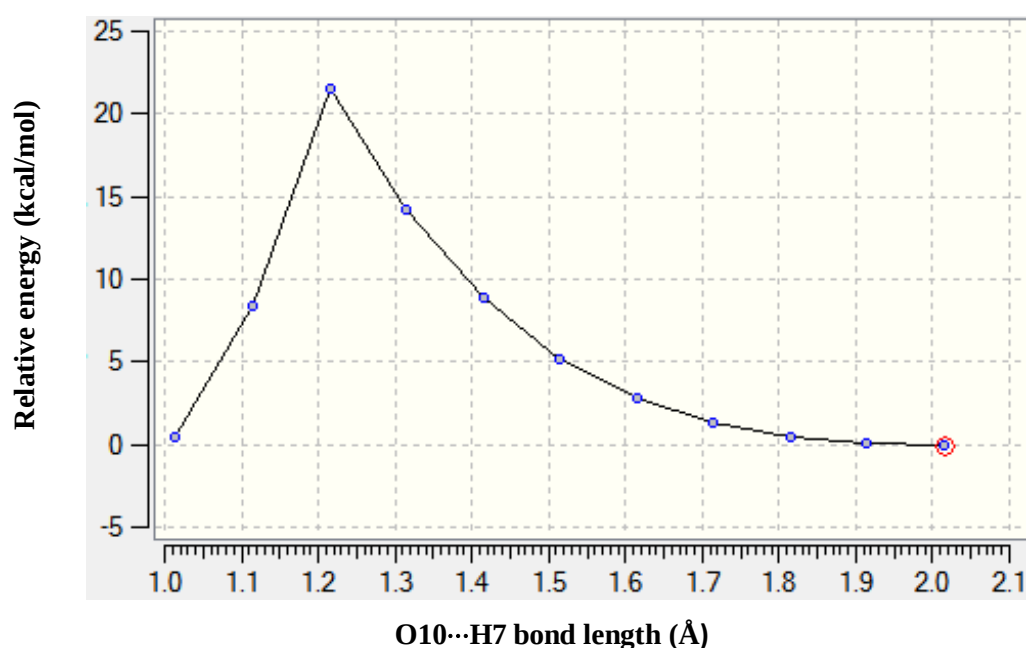


Figure 5.2: BHHLYP/6-31+G(d, p) scan (in steps of 0.1 Å) for the O10...H7 bond in the FG...•OOH reaction complex in order to abstract the phenolic H atom.

by one imaginary frequency of magnitude (cm^{-1}) of 2223.3 *in vacuo*, 2301.5 in benzene and 2811.7 ethanol. The geometries and the molecular graphs for TS and PC are shown in Figure 5.1 while the electronic properties at BCPs and relative energies are reported in Table 5.2 and Table 5.3, respectively.

The TS geometry is characterised by the presence of the O7–H7···O10 H-bond. O7–H7 is longer in the transition state than in the reactant complex while O10···H7 is shorter in the transition state than in the reactant complex, implying that the O7–H7 bond elongates while the O10···H7 bond shortens from reactant complex to transition state. The molecular graph for TS shows the existence of the O7–H7 bond, the O10···H7 bond and the C3···O11 bond, which form part of the six member ring. The O7–H7 bond has lower ρ in the transition state structure than in the reactant complex structure while O10···H7 has higher ρ value in the transition state structure than in the reaction complex structure, indicating that the electron density is less accumulated within the O7–H7 bond in TS than in RC while the electron density is more accumulated within the O11···H7 bond in TS than in RC. The $\nabla^2\rho$ and H values are all negative for both the O7–H7 and O10···H7 bonds, indicating that these bonds have strong interaction characters in nature; it is confirmed by the $|V|/G$ ratio values of 8.3 and 8.5 for the O7–H7 bond and the O10···H7 bond, respectively.

The geometry for PC is characterised by the interaction of the 4, 6-dihydroxylphenoxyl radical and H_2O_2 molecule, with the H_2O_2 molecule preferentially existing in the *cis* arrangement. The O7···H7 H-bond formed between 4, 6-dihydroxylphenoxyl radical and H_2O_2 molecule is longest in benzene solvent medium and shortest *in vacuum*, suggesting that the strength of the H-bond tends to decrease in the presence of the solvent molecules. The O7···H7 bond distance is significantly longer in the transition state structure than in the product complex structure, implying that the O7···H7 bond elongates from TS to PC. The molecular graph for PC confirms the existence of the O7···H7 intermolecular bond. The electron density value decreases significantly from TS to PC, implying that less electrons are accumulated within the O7···H7 bond in PC than in TS. The $\nabla^2\rho$ and H values are positive for the O7···H7 bond in PC, indicating that the O7···H7 bond has weak characters in nature.

The spin density distributions in PC are reported in Table 5.4; they provide information on the stability of 4, 6-dihydroxylphenoxyl. Studies have shown that the stability of the phenoxyl is largely dependent on the extent by which the spin density is distributed further away from the atom on which the phenolic H atom was abstracted [68, 283, 284]. The spin density distribution on O7 is lower *in vacuo* than in polar and in non-polar media.

Table 5.4: Spin density on selected atoms within the product complex species; M06–2X/6-311++G(3df,2p) results in different media

structure and media ^a	spin density ($e\text{\AA}^3$) on selected atoms				
	O7	C1	C3	C5	O11
(PC) _{FG}					
<i>in vacuo</i>	0.287	0.305	0.370	0.717	
in benzene	0.330	0.310	0.464	0.681	
in ethanol	0.290	0.303	0.384	0.716	
(PC) _{THAP1} ^b					
<i>in vacuo</i>	0.258	0.610	0.331	0.482	
in benzene	0.281	0.031	0.564	0.459	
in ethanol	0.245	0.020	–0.020	0.751	
(PC) _{THAP2} ^b					
<i>in vacuo</i>	0.327	0.361	0.146	0.731	0.078
in benzene	0.332	0.440	0.195	0.672	0.085
in ethanol	0.305	0.610	0.331	0.482	0.088

^a The abbreviation FG denotes phloroglucinol and THAP denotes phloracetophenone. O7, C1, C3, C5 and O11 are atoms within the given structure and their corresponding numbering

^b The numbers 1 and 2 on THAP denote the para phenolic OH and the ortho phenolic OH reaction sites with respect to the acyl group on THAP respectively.

The energy profile for FG + •OOH is shown in Figure 5.3. The ΔE_{act} (kcal/mol) value is 13.263 *in vacuo*, 13.602 in benzene and 14.399 in ethanol, implying that ΔE_{act} value does not depend on the dielectric constant of the media. The electronic energy of PC is lower than the total energy of the separate reactant molecules. However, its energy is not significantly different from the energy of RC. FG + •OOH is exothermic (when the enthalpy values for the product species are compared with those of the isolated reactant species). $\Delta G > 0$, indicating that FG + •OOH is endergonic in nature.

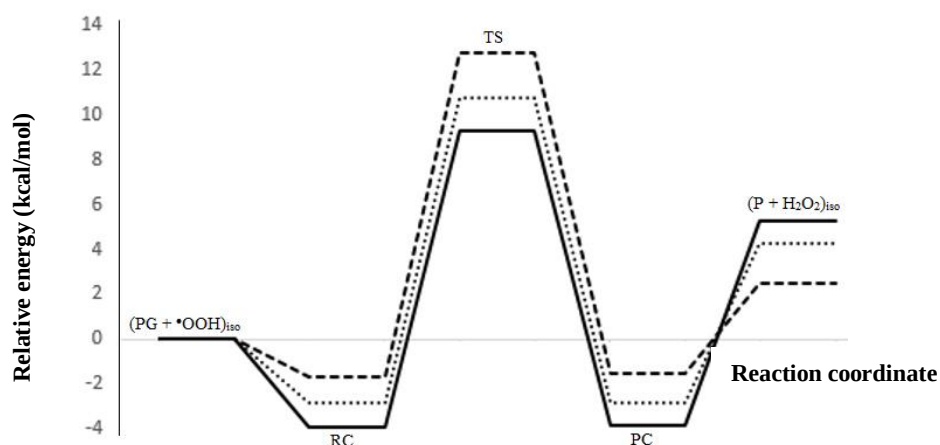


Figure 5.3: M06–2X/6-311++G(3df, 2p) energy profile (potential versus reaction coordinate) for the reaction of phloroglucinol with peroxy radical in vacuum (—), in benzene solvent medium (.....) and in ethanol solvent medium (-----). The acronym RC stands for reactant complex, TS stands for transition state, PC stands for product complex and P_{iso} stands for isolated product species.

The rate constant ($\text{M}^{-1} \text{s}^{-1}$) for FG + •OOH is reported in Table 5.5; it has a value of 3.593×10^2 in *vacuum*, 9.548 in benzene solvent medium and 2.751×10^1 in ethanol solvent medium, which indicates that FG + •OOH is likely to occur faster in *vacuum* than in the presence of the solvent medium. The results obtained are consistent with the ΔE_{act} in the analysis of the energetic properties.

Table 5.5: Reaction rate constants ($\text{M}^{-1} \text{s}^{-1}$) for FG + •OOH, THAP1 + •OOH and THAP2 + •OOH.

calculation method	results obtained using 6-31++G(d,p) basis set			results obtained using 6-311++G(3df,2p) basis set		
	<i>in vacuo</i>	in benzene	in ethanol	<i>in vacuo</i>	in benzene	in ethanol
apparent rate constant ^a for FG ^b + •OOH						
DFT/M06–2X	9.920×10^2	1.189×10^2	9.417	3.593×10^2	9.548	2.751×10^1
DFT/MPW1K	1.184	4.711	0.232	0.174	0.693	4.053
DFT/ BHHLYP	1.596×10^{-2}	5.400×10^{-2}	8.198×10^2	2.465×10^{-3}	6.092×10^{-3}	7.717×10^1
apparent rate constant ^a for THAP1 ^b + •OOH						
DFT/M06–2X	1.246×10^3	2.096×10^1	4.602×10^1	5.282×10^2	2.191×10^1	4.988×10^1
DFT/MPW1K	2.283	1.100	0.117	0.188	0.169	5.187×10^{-2}
DFT/ BHHLYP	1.456×10^{-2}	1.919×10^6	— ^c	2.057×10^{-3}	2.034×10^5	— ^c
apparent rate constant ^a for THAP2 ^b + •OOH						
DFT/M06–2X	2.589	9.035×10^{-2}	0.148	1.278	3.934×10^{-2}	5.946×10^{-2}
DFT/MPW1K	5.760×10^{-3}	1.534×10^{-3}	2.702×10^{-4}	1.018×10^{-3}	5.99×10^{-4}	3.275×10^{-5}
DFT/ BHHLYP	6.903×10^{-5}	2.759×10^{-5}	— ^c	2.294×10^{-5}	2.162×10^{-6}	— ^c

^a The K_D ($\text{M}^{-1} \text{s}^{-1}$) value used to calculate the apparent rate constant in benzene is 1.155×10^{10} and in ethanol is 6.341×10^9 .

^b The abbreviation FG stands for phloroglucinol and THAP stands for phloracetophenone. The number “1” attached to THAP denotes the *para* phenolic OH reaction site while the number “2” represents the *ortho* phenolic OH reaction site with respect to the acyl group on THAP.

^c The apparent rate constants for the THAP1 + •OOH reaction and the THAP2 + •OOH reaction were estimated only with DFT/M06–2X and DFT/MPW1K calculation methods.

5.3.2 THAP + •OOH reaction

This section presents and discusses results obtained for THAP1 + •OOH and THAP2 + •OOH. The resultant product from each reaction is the acylated 4, 6-dihydroxyphenoxy radical and hydrogen peroxide. Analysis of the results for the THAP1 + •OOH reaction are presented first followed by the discussion of the results for the THAP2 + •OOH reaction. The oxygen atom that is not covalently bonded to the hydrogen atom in •OOH is labelled O13 while the oxygen atom that is covalently bonded to the hydrogen atom in •OOH is labelled O14.

5.3.2.1 Geometric, energetic and kinetic properties for THAP1 + •OOH

THAP was utilised to interact with •OOH at the *ortho* position, resulting in the formation of the reactant complex. The reactant complex obtained is denoted throughout the study as RC^{τ} . The geometry of RC^{τ} and its corresponding molecular graph are shown in Figure 5.4; it has two hydrogen bonds, which are O7–H7...O13 and C3–H3...O14. O7–H7...O13 is shorter than C3–H3...O14. The O13...H7 bond distance is shorter while the O14...H3 bond distance is longer *in vacuo* than in polar and in non-polar media, implying that the O13...H7 bond shortens while the O14...H3 bond elongates with an increase in the dielectric constant of the media. The molecular graph for RC^{τ} shows the existence of the four rings; two 6-member rings and two 5-member rings. The electronic properties at BCPs for RC^{τ} are also reported in Table 5.2. The $\nabla^2\rho$ and H values are all positive for the O13...H7 bond and the O14...H3 bond, indicating that the two bonds have weak interaction characters in nature; it is confirmed by the $|V|/G$ values of 0.9 and 0.8 for the O13...H7 and the O14...H3 bonds, respectively.

The total energy and the relative energy for RC^{τ} are shown in Table 5.6 and Table 5.6, respectively. The energy of RC^{τ} is lower than the total energy of the separate reactant species, implying that the preferred starting geometry for THAP1 + •OOH is RC^{τ} compared to the isolated reactant species.

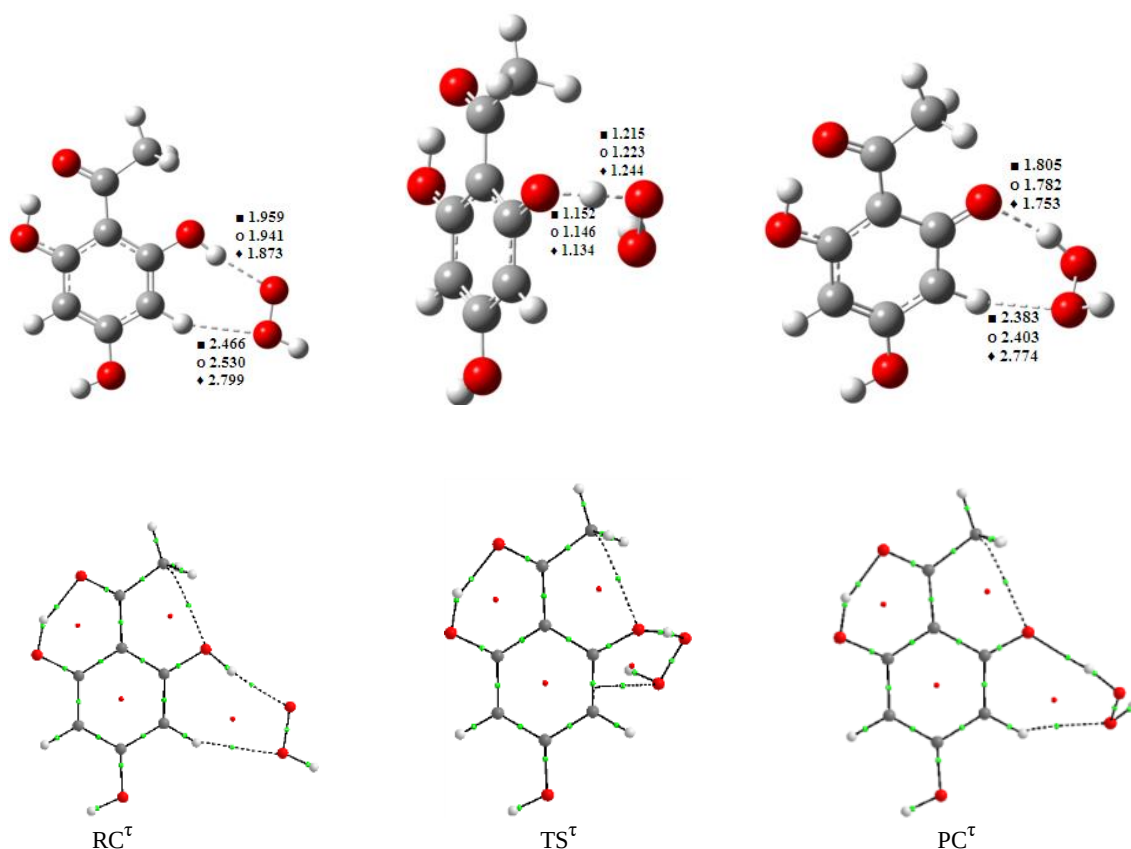


Figure 5.4: M06-2X/6-311++G(3df, 2p) geometries (first row) and the corresponding molecular graphs (second row) for the THAP1 + $\bullet$ OOH reaction species. Some selected bond lengths (Å) that are shown on the geometries correspond to results in vacuum (■), in benzene solvent medium (○) and in ethanol solvent medium (◆). The green dot within a given bond represents the bond critical point while the red dot within a given ring stands for the ring critical point.

Table 5.6: Relative electronic energy (ΔE , kcal/mol), enthalpy (ΔH , kcal/mol) and Gibbs free energy (ΔG , kcal/mol) for the THAP1^a + •OOH reaction species.

structure ^b	results obtained utilising the 6-31++G(d,p) basis set			results obtained utilising the 6-311++G(3df,2p) basis set		
	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative Gibbs free energy (ΔG , kcal/mol)	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative Gibbs free energy (ΔG , kcal/mol)
DFT/M06-2X results obtained <i>in vacuo</i>						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-5.333	-5.553	4.254	-4.708	-4.871	4.516
TS [‡]	7.300	6.825	17.452	8.217	7.753	18.222
PC [‡]	-5.371	-5.053	3.165	-4.873	-4.554	3.662
(P [‡] + H ₂ O ₂) _{iso}	3.130	3.301	2.661	2.984	3.150	2.556
DFT/M06-2X results obtained in benzene solvent medium						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-5.053	-5.029	4.233	-4.987	-5.024	4.750
TS [‡]	9.412	8.960	19.677	10.233	9.804	20.341
PC [‡]	-3.806	-3.424	4.831	-3.436	-3.065	5.161
(P [‡] + H ₂ O ₂) _{iso}	2.869	3.096	2.249	2.714	2.931	2.140
DFT/M06-2X results obtained in ethanol solvent medium						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-1.952	-1.739	7.019	-2.145	-2.432	7.810
TS [‡]	11.999	11.632	22.171	12.691	12.291	22.914
PC [‡]	-2.076	-1.719	6.812	-1.968	-1.568	6.744
(P [‡] + H ₂ O ₂) _{iso}	1.870	2.168	1.216	1.908	2.183	1.303
DFT/MPW1K results obtained <i>in vacuo</i>						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-4.059	-3.783	4.367	-3.515	-3.168	4.176
TS [‡]	11.162	10.734	21.298	12.494	12.080	22.587
PC [‡]	-4.116	-3.825	4.817	-3.304	-2.973	5.439
(P [‡] + H ₂ O ₂) _{iso}	2.539	2.752	1.980	2.839	3.049	2.290
DFT/MPW1K results obtained in benzene solvent medium						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-2.615	-2.386	5.980	-2.166	-1.914	6.401
TS [‡]	13.304	12.887	23.343	14.564	14.110	24.874
PC [‡]	-2.802	-2.486	5.895	-1.970	-1.563	5.759
(P [‡] + H ₂ O ₂) _{iso}	2.437	2.652	1.828	2.749	2.963	2.152
DFT/MPW1K results obtained in ethanol solvent medium						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-0.909	-0.705	8.084	-0.717	-0.275	7.525
TS [‡]	16.216	15.766	26.776	17.005	16.835	26.699
PC [‡]	-1.454	-1.002	6.738	-0.747	-0.141	7.239
(P [‡] + H ₂ O ₂) _{iso}	1.423	1.660	1.030	1.811	2.247	0.920
DFT/BHLYP results obtained <i>in vacuo</i>						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-4.153	-3.876	4.359	-3.621	-3.292	4.469
TS [‡]	14.118	13.676	24.285	15.510	15.110	25.555
PC [‡]	-5.645	-5.346	3.331	-4.556	-4.231	4.243
(P [‡] + H ₂ O ₂) _{iso}	1.458	1.664	0.926	-8.126	-7.925	-8.645
DFT/BHLYP results obtained in benzene solvent medium						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000

RC [‡]	8.856	9.144	17.348	8.928	9.260	17.011
TS [‡]	16.061	15.626	26.198	17.331	16.953	27.190
PC [‡]	-4.298	-4.002	4.730	-3.267	-2.966	5.664
(P [‡] + H ₂ O ₂) _{iso}	1.228	1.439	0.641	1.621	1.816	1.065
DFT/BHLYP results obtained in ethanol solvent medium						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-1.310	-0.954	7.321	-1.012	-0.631	7.294
TS [‡]	— ^c	— ^c	— ^c	— ^c	— ^c	— ^c
PC [‡]	-3.028	-4.172	8.182	-2.480	-2.006	5.643
(P [‡] + H ₂ O ₂) _{iso}	-0.235	0.049	-0.868	0.328	0.590	-0.277

^aThe number '1' on phloracetophenone represents the *ortho* phenolic OH reaction site with respect to the acyl group.

^bThe abbreviation RC[‡] stands for reactant complex, TS[‡] stands for transition state, PC[‡] stands for product complex and P[‡]_{iso} stands for isolated product species.

^cTS in ethanol was not obtained utilising DFT/BHLYP, the free phenolic hydrogen quickly went back to form RC[‡] in the THAP1 + •OOH reaction

The O13...H9 bond scan was performed starting from RC[‡] until the formation of acylated 4, 6-dihydroxyphenoxyl radical and H₂O₂. The outcome of the scan is shown in Figure 5.5; it shows the existence of the two minimum points and one maximum point. The first minimum point is located at the O13...H9 bond distance of 1.986 Å while the second minimum point is located at the O13...H9 bond distance of 0.986 Å. The two structures at each minimum point were optimised individually and the frequency calculations were performed on the optimised structures. Zero imaginary frequencies were obtained for individual structures located at the two minimum points. The structure at the first minimum point relates to RC[‡] while the structure at the second minimum point relates to the product complex. The product complex is represented as PC[‡] throughout the study. The structure at the maximum point was found at the O13...H9 bond distance of 1.186 Å. It was separately optimised and then frequency calculations were performed on the optimised structure; one imaginary frequency of magnitude (cm⁻¹) 2211.3 *in vacuo*, 2333.6 in benzene and 2879.2 in ethanol was obtained, indicating that it is a transition state on PES. The transition state is denoted as TS[‡]. The geometries and the corresponding molecular graphs for TS[‡] and PC[‡] are also shown in Figure 5.4 while their electronic properties at BCPs and relative energies for TS[‡] and PC[‡] are reported in Table 5.2 and Table 5.6, respectively.

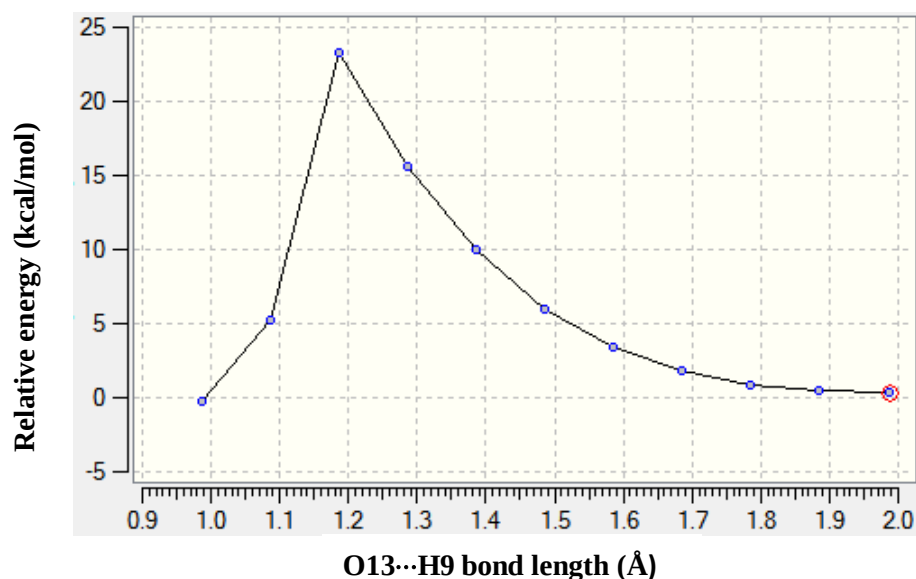


Figure 5.5: O13...H9 bond scan (in steps of 0.1Å) for the reaction of THAP1 + •OOH. Results obtained utilising BHHLYP/6-31+G(d, p) basis set *in vacuo*.

The TS[‡] geometry has O7–H7...O13 hydrogen bond. The O7–H7 bond has a longer distance in TS[‡] than in RC[‡] while the O13...H7 bond has a shorter distance in TS[‡] than in RC[‡], indicating that the O7–H7 bond elongates while the O13...H7 bond shortens from RC[‡] to TS[‡]. The molecular graph for TS[‡] shows the existence of the O7–H7 bond and the O13...H7 bond, which forms part of the five member ring. The $\nabla^2\rho$ value is positive while the H value is negative for the O13...H7 bond, implying that the O13...H7 bond has both weak and strong interaction characteristics.

The geometry for PC[‡] is characterised by the existence of the hydrogen bond between acylated 4, 6-dihydroxyphenoxy radical and H₂O₂. Analysis of the O7...H7 bond distance obtained in different media suggests that it does not depend on the dielectric constant of the media. The molecular graph shows the presence of four rings, each ring is confirmed by ring critical point. The $|V|/G$ ratio value is 1.0 for the O7...H7 bond, implying that it has characters of a weak bond.

The energy profile for the THAP1 + $\bullet$ OOH reaction is shown in Figure 5.6; ΔE_{act} (kcal/mol) is 12.925 *in vacuum* medium, 15.220 in benzene solvent medium and 14.836 in ethanol solvent medium, implying that THAP1 + $\bullet$ OOH is expected to occur faster *in vacuum* than in the presence of the solvent. A comparison of the electronic energy gap between the energy of the product complex and the isolated reactant species indicates that THAP1 + $\bullet$ OOH is exothermic. However, the energy of the product complex is not significantly different from the energy of RC. ΔG (kcal/mol) value is -0.854 *in vacuum*, 0.411 in benzene solvent medium and -1.066 in ethanol solvent medium.

The rate constant for THAP1 + $\bullet$ OOH is reported in Table 5.5; it is denoted as k^{τ} . The value of k^{τ} ($\text{M}^{-1} \text{s}^{-1}$) is 5.282×10^2 , 2.191×10^1 and 4.988×10^1 , indicating that THAP1 + $\bullet$ OOH preferably occurs faster *in vacuum* medium than in the presence of the solvent.

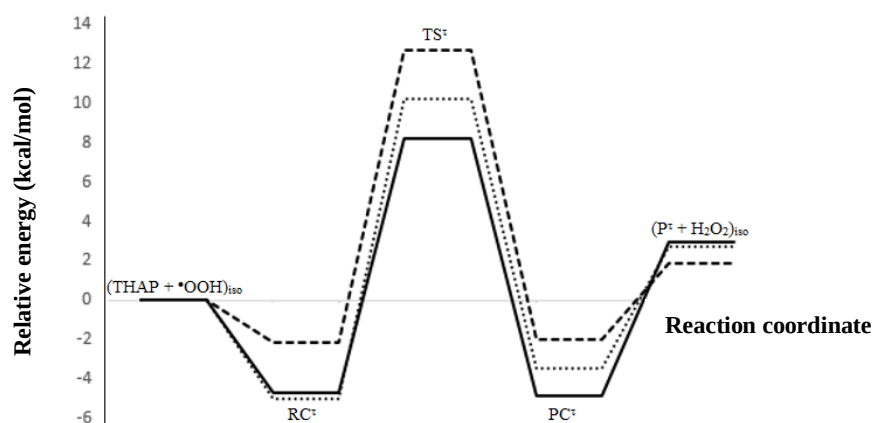


Figure 5.6: M06–2X/6-311++G(3df, 2p) energy profile (potential energy versus reaction coordinate) for the THAP1 + $\bullet$ OOH reaction in vacuum medium (—), in benzene solvent medium (.....) and in ethanol solvent medium (-----). The acronym RC^{τ} denotes reactant complex, TS^{τ} represents transition state, PC^{τ} represents product complex and $\text{P}^{\tau}_{\text{iso}}$ denotes isolated product species.

5.3.2.2 Geometric, energetic and kinetic properties for THAP2 + $\bullet$ OOH

THAP2 + $\bullet$ OOH was achieved by interacting THAP with $\bullet$ OOH at the *para* position, resulting in the reactant complex. The reactant complex is denoted as RC ‡ ; the geometry and the corresponding molecular graph are shown in Figure 5.7; the complex has two hydrogen bonds, which are O13 $\cdots$ H8 and O14 $\cdots$ H5. The O13 $\cdots$ H8 bond distance is longer in ethanol than *in vacuo* and in benzene, indicating that the O13 $\cdots$ H8 bond tends to elongate in the presence of a polar medium. The molecular graph confirms the existence of the two intermolecular H-bonds. The electronic properties at BCPs are reported in Table 5.2. The $\nabla^2\rho$ and H values are positive for O13 $\cdots$ H8 bond and O14 $\cdots$ H5, implying that the two bonds are weak in nature. The total energies and the relative energies for RC ‡ are reported in Table 5.7 and Table 5.8, respectively. RC ‡ has lower electronic energy than the total electronic energies for the separate reactant species, indicating that the preferred starting geometry for THAP2 + $\bullet$ OOH is also a reactant complex.

The scan was performed starting from RC ‡ in order to obtain 2, 6-dihydroxyphenoxy radical and hydrogen peroxide. The scan for the abstraction of H8 in RC ‡ , in order to form the 2, 6-dihydroxyphenoxy radical, is shown in Figure 5.8; it is characterised by the two minimum points and one maximum point. The two minimum points are located at the O13 $\cdots$ H8 bond distance of 1.871 Å and 0.971 Å while the maximum point is located at a bond distance of 1.171 Å. Optimisation followed by frequency calculations upon structures found at the minimum points gave zero imaginary frequencies, indicating that they are both minima in PES. The structure at the minimum point located at the O13 $\cdots$ H8 bond distance of 1.871 Å is RC ‡ while the structure at the minimum point located at 0.971 Å corresponds to the product complex. The product complex is denoted as PC ‡ . In order to locate the transition state, structure at the maximum was also optimised separately followed by frequency calculations; one imaginary frequency (of magnitude (cm $^{-1}$) 2253.5 *in vacuo*) was obtained, implying that the structure at the maximum is a transition state on PES. The transition state is denoted as TS ‡ . The geometries and the corresponding molecular graphs for PC ‡ and TS ‡ , are also shown in Figure 5.7 while their electronic properties at BCPs and relative energies are reported in Table 5.2 and Table 5.7, respectively.

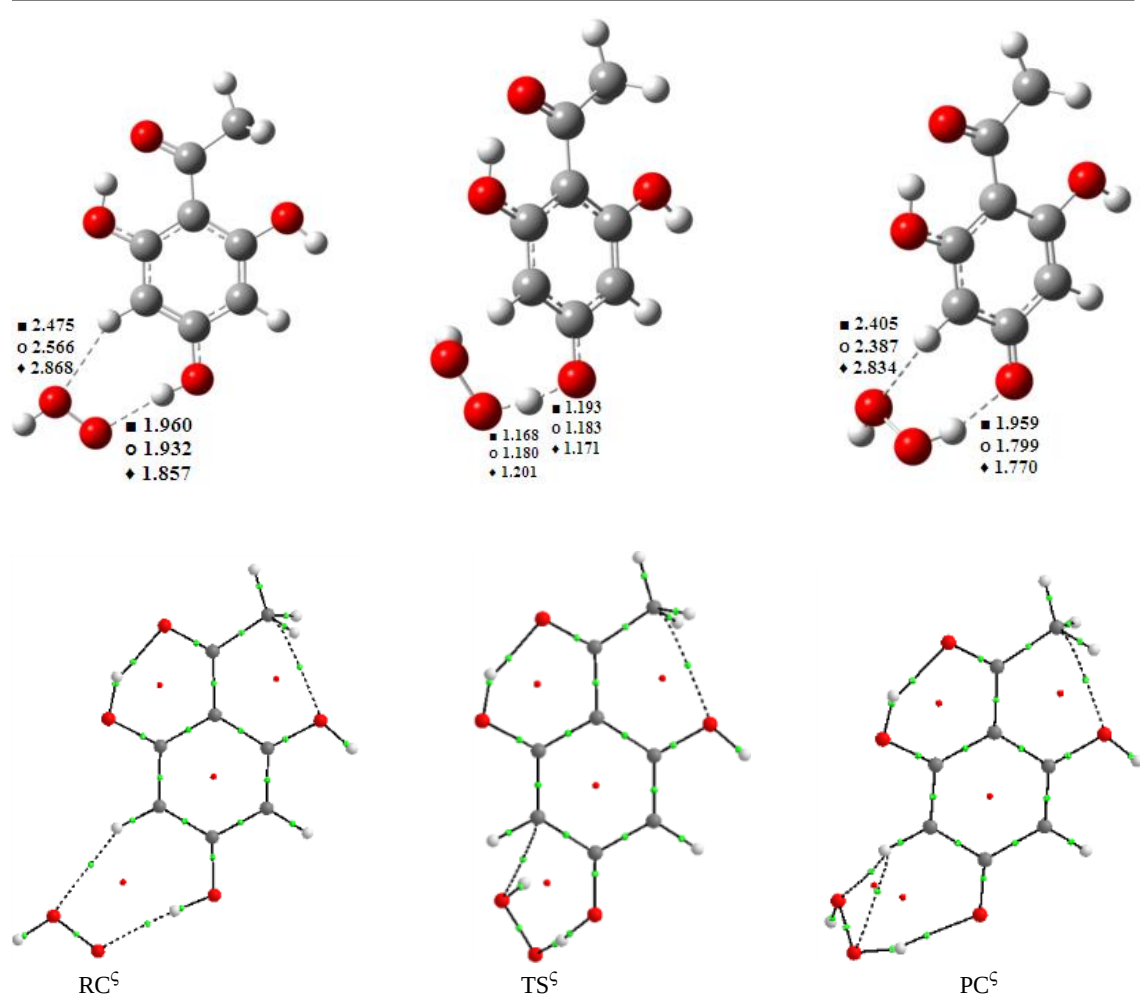


Figure 5.7: M06-2X/6-311++G(3df, 2p) geometries (first row) and the corresponding molecular graphs (second row) for the THAP2 + •OOH reaction species. Some selected bond lengths (Å) that are shown on the geometries correspond to results *in vacuo* (■), in benzene (○) and in ethanol (◆). The green dot within a given bond represents the bond critical point while the red dot within a given ring denotes the ring critical point.

Table 5.7: Relative electronic energy (ΔE , kcal/mol), enthalpy (ΔH , kcal/mol) and Gibbs free energy (ΔG , kcal/mol) for the THAP2^a + •OOH reaction species.

structure ^b	results obtained utilising 6-31++G(d,p) basis set			results obtained utilising 6-311++G(3df,2p) basis set		
	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative Gibbs free energy (ΔG , kcal/mol)	relative electronic energy (ΔE , kcal/mol)	relative enthalpy (ΔH , kcal/mol)	relative Gibbs free energy (ΔG , kcal/mol)
DFT/M06-2X results obtained <i>in vacuo</i>						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-5.260	-5.450	4.102	-4.609	-4.780	4.509
TS [‡]	10.824	10.367	20.959	11.947	11.545	21.784
PC [‡]	1.327	1.684	9.512	2.017	2.359	10.198
(P [‡] + H ₂ O ₂) _{iso}	9.293	9.480	8.306	9.371	9.009	9.726
DFT/M06-2X results obtained in benzene solvent medium						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-3.732	-3.328	4.066	-3.255	-2.860	4.504
TS [‡]	12.802	12.378	22.911	13.758	13.336	23.840
PC [‡]	2.705	3.067	11.330	3.129	3.578	11.011
(P [‡] + H ₂ O ₂) _{iso}	8.927	9.170	7.706	8.9150	8.595	9.151
DFT/M06-2X results obtained ethanol solvent medium						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-2.131	-1.826	6.783	-1.999	-1.778	6.989
TS [‡]	15.440	15.080	25.334	16.264	15.863	26.082
PC [‡]	4.144	4.141	13.243	4.531	4.996	13.018
(P [‡] + H ₂ O ₂) _{iso}	8.178	7.901	8.426	8.089	8.456	7.087
DFT/MPW1K results obtained <i>in vacuo</i>						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-4.000	-3.712	4.355	-3.424	-3.106	4.730
TS [‡]	14.890	14.472	24.830	16.319	15.913	26.233
PC [‡]	3.010	3.302	11.544	4.242	4.603	12.390
(P [‡] + H ₂ O ₂) _{iso}	9.313	9.472	8.485	9.857	10.048	8.829
DFT/MPW1K results obtained in benzene solvent medium						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-2.647	-2.349	5.673	-2.188	-1.887	6.365
TS [‡]	16.948	16.529	26.932	18.239	17.833	28.181
PC [‡]	4.316	4.646	12.502	5.309	5.727	13.017
(P [‡] + H ₂ O ₂) _{iso}	9.004	9.186	7.967	9.499	9.713	8.134
DFT/MPW1K results obtained in ethanol solvent medium						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-0.989	-0.698	7.714	-0.793	-0.245	7.000
TS [‡]	19.650	19.216	30.002	20.755	20.510	30.538
PC [‡]	5.398	5.859	13.684	6.063	6.778	13.838
(P [‡] + H ₂ O ₂) _{iso}	8.241	8.475	7.183	8.742	8.990	8.134
DFT/BHLYP results obtained <i>in vacuo</i>						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-4.153	-3.876	4.359	-4.305	-4.295	5.170
TS [‡]	17.565	17.160	27.455	19.074	18.682	28.919
PC [‡]	1.045	1.361	9.421	2.294	2.668	10.270
(P [‡] + H ₂ O ₂) _{iso}	7.632	7.787	6.813	-1.712	-1.529	-2.730
DFT/BHLYP results obtained in benzene solvent medium						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-2.653	-2.369	5.686	-2.263	-1.935	5.584
TS [‡]	19.450	19.040	29.327	20.846	20.438	30.733

PC [‡]	2.275	2.551	11.056	3.320	3.669	11.694
(P [‡] + H ₂ O ₂) _{iso}	7.230	7.360	6.658	7.792	7.936	7.167
DFT/BHLYP results obtained in ethanol solvent medium						
(THAP + •OOH) _{iso}	0.000	0.000	0.000	0.000	0.000	0.000
RC [‡]	-1.310	-0.954	7.321	-1.012	-0.632	7.294
TS [‡]	— ^c	— ^c	— ^c	— ^c	— ^c	— ^c
PC [‡]	3.008	3.499	10.845	3.590	4.215	11.317
(P [‡] + H ₂ O ₂) _{iso}	5.963	5.662	6.214	6.372	6.704	5.311

^a The abbreviation THAP denotes phloracetophenone; the number “2” attached to THAP denotes the *para* phenolic OH reaction site with respect to the acyl group.

^b The abbreviation RC[‡] stands for the reactant complex, TS[‡] stands for the transition state, PC[‡] stands for the product complex and P[‡]_{iso} isolated product species.

^c TS[‡] geometry in ethanol for THAP2 + •OOH was obtained using DFT/M06-2X and DFT/MPW1K calculation methods.

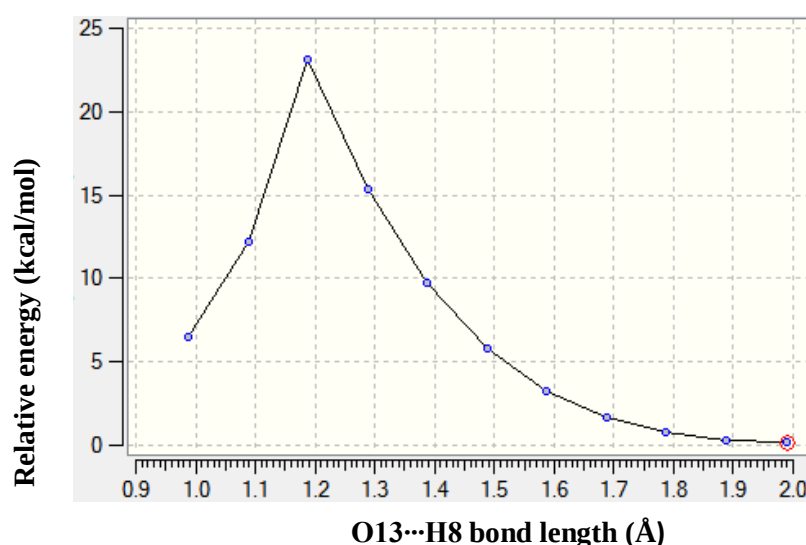


Figure 5.8: O13...H8 bond scan (in steps of 0.1 Å) for the reaction of THAP2 + •OOH. Results obtained utilising BHLYP/6-31+G(d, p) basis set *in vacuo*.

The TS[‡] geometry has the O8...H8 and the O13...H8 bonds. The O13...H8 bond distance is shorter in TS[‡] than in RC[‡], indicating that the O13...H8 bond tends to shorten in moving from RC[‡] to TS[‡]. The molecular graph confirms the presence of the O8...H8 bond and the O13...H8 bond, forming part of the seven member ring. The ρ value for the O13...H8 bond decreases from RC[‡] to TS[‡], indicating that electron density is more accumulated within the O13...H8 bond in TS[‡] than in RC[‡]. The $\nabla^2\rho$ and H are negative for the O13...H8

bond in TS[‡], suggesting that the O13...H8 bond has strong interaction characters in nature; the V/G ratio is 3.3.

PC[‡] is formed by the interaction between acylated 2, 6-dihydroxyphenoxyl radical and H₂O₂. The O8...H8 bond is longer in PC[‡] than TS[‡], implying that the O8...H8 bond tends to elongate in moving from TS[‡] to PC[‡]. The molecular graph shows the presence of the O8...H8 bond and the O14...H5 bond, which forms part of the seven member ring. The ρ value for the O8...H8 bond decreases from TS[‡] to PC[‡], indicating that the electron density is less accumulated within the O8...H8 bond in PC[‡] than in TS[‡].

The energy profile for THAP2 + •OOH is shown in Figure 5.9; the ΔE_{act} (kcal/mol) value is 16.727 *in vacuo*, 17.013 in benzene and 18.263 in ethanol, suggesting that THAP2 + •OOH preferably occurs faster *in vacuum* than in the absence of the solvent molecules. The ΔH between PC[‡] and RC[‡] is positive, which indicates THAP2 + •OOH is endothermic. The ΔG value between PC[‡] and RC[‡] is also positive, implying that THAP2 + •OOH is endergonic.

The rate constant for the THAP2 + •OOH reaction is reported in Table 5.6; it is denoted as $k^{\ddagger}$ and has a value ($\text{M}^{-1} \text{s}^{-1}$) of 1.278 *in vacuo*, 3.934×10^{-2} in benzene and 5.946×10^{-2} in ethanol, implying that THAP2 + •OOH has a tendency to occur faster *in vacuum* than in polar and non-polar media. The results obtained are consistent with the analysis of the energetic properties, which shows that the activation energy is lowest *in vacuo*.

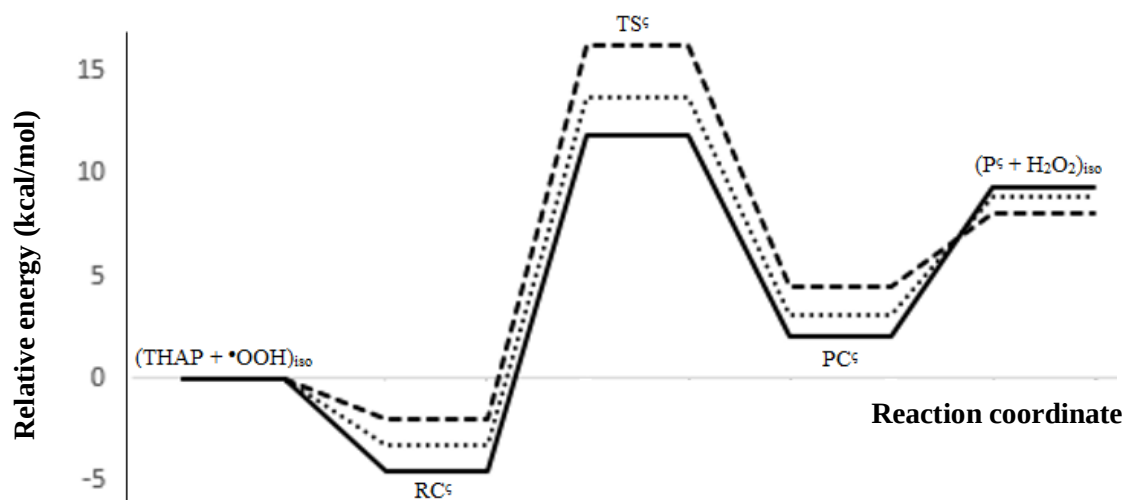


Figure 5.9: M06–2X/6-311++G(3df, 2p) energy profile (potential energy versus reaction coordinate) for the THAP2 + $\bullet\text{OOH}$ reaction in vacuum (—), in benzene solvent medium (.....) and in ethanol solvent medium (-----) media. The acronyms $\text{RC}^\ddagger$ denotes reactant complex, $\text{TS}^\ddagger$ represents transition state, $\text{PC}^\ddagger$ represent product complex and $\text{P}^\ddagger_{\text{iso}}$ denotes isolated product species.

5.4 Assessment on the performance of the calculation methods

An assessment of the performance of the selected calculation methods can be performed through analysis of their ability to estimate the reaction enthalpies and barrier heights. The comparison of their performance can be assessed in terms of how far the values obtained from the different methods deviates from each other or by comparison with standard benchmark methods.

An assessment of the ability of the different methods to estimate the different reaction enthalpy values in different media suggests that DFT/BHLYP method tends to significantly underestimate the values of the various reaction enthalpies with respect to the values obtained using the DFT/M06–2X method. DFT/MPW1K results remains mostly close to the values obtained using the DFT/M06–2X method [284].

The ability of the methods to estimate the barrier height for the different steps of the various reaction pathways was assessed by using the CBS-QB3 compound method as a benchmark method. The results of the comparison between the DFT methods utilised in this study and the CBS-QB3 method are reported in Table 5.8; DFT/M06–2X method tends to estimate the barrier height with values that are close to the values obtained using CBS-QB3 method while DFT/BHLYP method tends to significantly underestimate the barrier heights with respect to the selected benchmark method; the ability of the DFT/MPW1K to estimate the barrier heights lies between the two methods, albeit being closer to the DFT/M06–2X method than to the DFT/BHLYP method. In this regard, the trends obtained for the barrier heights in this chapter are similar to those obtained in section 4.5, although in that case, the benchmark method was not utilised in the assessment of the methods.

Assessment of the effect of the 6-31++G(d,p) basis set and the 6-311++G(3df,2p) basis set in the estimation of the barrier height indicates that the difference in the barrier heights between the selected basis sets lies within the 1–1.5 kcal/mol range, with the extended basis set predicting a higher barrier height than the standard basis set. A similar trend was also obtained on the study involving $\bullet\text{OH}$ (section 4.5). Therefore, an assessment of the effect of the basis sets on the studies reaction mechanism in their ability to estimate the barrier heights suggests that there is no large influence of the basis set in this property.

Table 5.8: Comparison of the barrier heights (kcal/mol) for FG + $\bullet\text{OOH}$ and THAP1 + $\bullet\text{OOH}$, results obtained utilising different calculating methods.

calculation method	<i>in vacuo</i>	in benzene	in ethanol	<i>in vacuo</i>	in benzene	in ethanol
	results obtained for the reaction of FG + $\bullet\text{OOH}$			results obtained for the reaction of THAP1 + $\bullet\text{OOH}$		
CBS-QB3	15.760	16.292	14.937	14.196	15.499	
DFT/M06–2X	13.934	16.084	15.456	13.706	15.591	15.104
DFT/MPW1K	18.455	17.638	19.714	18.411	18.473	19.174
DFT/BHLYP	20.978	20.442	14.845	21.086	10.179	— ^a

^aTransition state in ethanol was not obtained utilising BHLYP, the free phenolic hydrogen quickly went back to form RC in the THAP + OOH reaction.

5.5 Summary of the chapter

The results obtained for the FG + $\bullet$ OOH reaction and the THAP + $\bullet$ OOH reaction have been presented in this chapter in terms of reaction enthalpies describing the hydrogen atom transfer mechanism (HAT) and the two electron transfer mechanisms (i.e., single electron-proton transfer (SET-PT) and the sequential proton-loss electron-transfer mechanisms (SPLET)). The outcome of the findings on the reaction enthalpies suggests that the HAT mechanism is preferred to both SET-PT and SPLET mechanisms. However, although the HAT mechanism is the most preferred, it is slightly endothermic in nature and it is more preferred in polar medium than in non-polar medium for results obtained using the DFT/M06-2X and the DFT/MPW1K methods. THAP is a better $\bullet$ OOH scavenger than FG through the HAT mechanism. The most preferred site within the THAP molecule for scavenging $\bullet$ OOH is the free phenolic OH group at the *ortho* position.

The HAT mechanism was studied further by investigating the reaction mechanism for the abstraction of the phenolic H atom in FG and THAP by $\bullet$ OOH. The geometric features, the energetic properties and kinetic properties for the mechanism were analysed for the reaction involving both compounds. The findings of the study suggests both reactions are initiated from a pre-reaction complex structure and that the final product structure is also preferably in a complex form rather than isolated product species. There is minimal energy difference between the pre-reactive complex and the product complex structure. Finally, the findings suggests that kinetically, THAP + $\bullet$ OOH reaction is preferred to FG + $\bullet$ OOH reaction. The findings reported in this chapter are therefore consistent with the experimental findings on the study of these compounds [69].

CHAPTER 6

CONCLUSIONS AND FUTURE RECOMMENDATIONS

6.1 Conclusions

A theoretical study on the reactions of phloroglucinol (FG) and phloroacetophenone (THAP) with $\bullet\text{OH}$ and $\bullet\text{OOH}$ have been performed through consideration of the hydrogen atom transfer (HAT), single electron-proton transfer (SET-PT), sequential proton-loss electron-transfer (SPLET) and oxidation mechanisms. The aim of the study has been to determine the preferred reaction mechanism in relation to radical scavenging properties of selected phloroglucinol molecules. The objective of the study has been to determine the reaction enthalpies (for the HAT, SET-PT and SPLET mechanisms), geometric, electronic, energetic and kinetic properties (for the HAT and oxidation mechanism) for the reactions. The study also intended to elucidate the preferred reactive site for the THAP molecule and to compare the radical scavenging properties of FG and THAP compounds in order to establish factors accounting for the preference of acylated phloroglucinol with respect to the parent compound.

The study has been performed *in vacuo*, in benzene and in ethanol media; the study *in vacuo* simulates reactions taking place in the atmosphere while the study in benzene and in ethanol simulate radical scavenging reactions taking place in non-polar and in polar media within the biological system. Meta-hybrid DFT functionals; M06-2X, MPW1K and BHHLYP have been utilised for calculations because they contain 54%, 42.8% and 50%, respectively of HF-like exchange. The standard 6-31++G(d,p) basis set and the extended 6-311++G(3df,2p) basis set have been utilised for the study to determine the dependency of the estimated properties on the basis sets utilised. The CBS-QB3

compound method have been used to benchmark the selected DFT functionals through analysis of the reaction barrier heights.

A comparison of the reaction enthalpy values suggests that for both compounds, the preferred reaction mechanism is the HAT mechanism. The HAT mechanism is thermodynamically preferable for the reaction of phloroglucinols with $\bullet\text{OH}$ than with $\bullet\text{OOH}$. A comparison of the two reactive sites, the *ortho* and the *para* sites, within the THAP molecule indicates that the *ortho* reactive site is the preferred site for interaction with the radical species. The bond dissociation enthalpies for THAP molecule are lower than those for FG, suggesting that it is a better radical scavenger than FG.

The hydrogen atom transfer mechanism has been shown to occur through three mechanism for the reactions involving $\bullet\text{OH}$ and only one mechanism for the reaction involving $\bullet\text{OOH}$. In the case of the reactions involving $\bullet\text{OH}$, the three mechanisms are the direct hydrogen atom transfer mechanism, the addition-elimination mechanism and the oxidation mechanism. However, the direct hydrogen atom transfer mechanism has been conclusively shown to have minimal contribution to the yield of the products, since it has negligible branching ratio with respect to the phenoxyl radical formed from the addition-elimination mechanism. The addition-elimination has been shown to preferably occur in the presence of the catalyst (e.g., a base catalyst) while the oxidation mechanism preferentially occurs in the presence of the oxygen molecule. The hydrogen atom transfer mechanism involving $\bullet\text{OOH}$ has been shown to proceed rather through the direct hydrogen atom transfer mechanism. Phloroacetophenone has shown to be a better $\bullet\text{OOH}$ scavenger than phloroglucinol. The preferred site for scavenging the radical species is the *ortho* phenolic OH site of phloroacetophenone.

The media plays a significant role in influencing the thermodynamic and the kinetic preference for the different reaction pathways. For instance, the isomerisation of the *keto* product obtained from the oxidation pathway is most preferred to occur *in vacuo* and least preferred to occur in ethanol. However, the high barrier height determined for the isomerisation process suggests that such a reaction (i.e., oxidation reaction leading to high order polyphenol derivative) can only occur at high temperature, indicating that such a

reaction is least likely to occur in the atmosphere, where the conditions are close to room temperature.

A comparison of the selected DFT methods indicates that DFT/M06–2X method gives barrier heights for the reactions involving $\bullet\text{OOH}$ which are closer to the barrier heights obtained using CBS-QB3 compound method, indicating that the DFT/M06–2X method better estimates the barrier height than the DFT/MPW1K and DFT/BHLYP methods.

Overall, the study presented in this dissertation has provided a thorough assessment of the reaction mechanisms involving phloroglucinol and its acylated derivative. These two compounds serve as moieties for large family of phloroglucinol derivatives and acylated phloroglucinol derivatives; for this reason, the results obtained in this dissertation could serve as starting point for understanding the reaction mechanisms of other phloroglucinols that can be utilised as radical scavengers. The outcome of the theoretical findings reported herein has also been compared (on several occasions) with available experimental data on the studied compounds; it has been shown that there is high correlations in the trends for the theoretical results reported in this work and experimental findings, on the compounds and other phenolic derivatives with similar features, reported elsewhere. For instance, it has been established both theoretically (in this dissertation) and experimentally that the addition mechanism is the preferred pathway for the formation of the phenoxyl radical species on the interaction of phloroglucinol with hydroxyl radical species.

6.2 Future recommendations

The work presented in this dissertation has been exhaustive in terms of assessment of the number of mechanisms through which phloroglucinol may interact with radical species. The study has considered not only two different but yet important radical species in the study, but also it has taken into consideration three different media; vacuum, non-polar medium and polar medium. The study has been performed by utilising the density functional theory, which is known to take into consideration dynamic correlations in the

description of the systems under study. Moreover, three hybrid functionals (two GGA and a meta-GGA) have been utilised in the study along with either the 6-31++G(d,p) basis set or the 6-311++G(3df,2p) basis set.

However, despite being an exhaustive study, a number of improvements may still be recommendable for future study on similar compounds in order to have a more rigorous assessment of the reactions of phloroglucinols and biologically relevant radical species. The first recommendation would be the fact that the selected computational methods could be enhanced by including methods that take into account static effect, such as the complete active space (CAS) methods. The reason for suggesting that such methods should be included among the methods that are utilised to study reactions involving radical species is the fact that radical species are largely doublet systems, with a single electron occupying the highest occupied orbital. The description of the orbitals with single electron occupancy are better described by methods that account for strong static correlation rather than dynamic correlation.

A second recommendation for future study would be to vary the basis set utilised in the study. In the current study, only the Pople's type basis set have been utilised, however, a better assessment of the basis set effects on the properties of the molecules is better performed by including other types of basis sets, for example the Dunning's correlation consistent basis sets could be utilised.

The third recommendation that is significant concerns the selection of the media in which the reaction is performed. In the current study, the polar medium selected is ethanol. This medium, although often utilised in experimental studies concerning antioxidant molecules capable of scavenging radical species, is not polar enough to describe all the biological environment in which antioxidant species are likely to interact with biologically relevant radical species. It is advisable therefore, that instead of mimicking only the environment utilised by experimentalist to study antioxidant molecules, future studies consider performing theoretical investigations in the presence of an aqueous medium, which is a suitable medium for mimicking the polar medium found within the biological system.

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